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Original Articles

STUDIES ON POLLEN AND POLLEN EXTRACTS

XI. THE CHEMICAL NATURE OF POLLEN ALLERGENS*

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IN AN earlier paper in this series[1] it was pointed out that most of the active fractions prepared from pollens in these laboratories have shown positive response to the Molisch test. Whether or not this fact had any significance from an immunologic point of view was not known at the time.

Black[2] first reported the isolation of an active polysaccharide fraction from ragweed pollen. This material was shown to react in higher dilution than an extract of whole pollen when tested intradermally or intranasally on a sensitive individual.

Disagreeing with Black's conclusion that the carbohydrate of ragweed pollen is specifically important, Stull, Cooke and Chobot[3] prepared highly purified protein fractions from giant and short ragweed pollens, which were negative to the Molisch test and which completely desensitized passively sensitized sites to later tests with the whole pollen extract. The purified protein solution was likewise found to be efficacious in the treatment of hypersensitive patients.

Our present investigation was undertaken with the view of determining which of the two above mentioned theories is correct.

EXPERIMENTAL

A. Chemical.—Preparation of the material for testing.

A preliminary study was made to determine the concentration of alcohol necessary for complete precipitation of the active polysaccharide fraction. Giant and short ragweed pollens were used. Twenty grams

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of each pollen were extracted with 200 c.c. water in divided portions, the extracts filtered by suction and combined. The filtrate was then treated with a few drops of acetic acid and brought to boiling. The precipitate was filtered off and the filtrate evaporated in vacuo practically to dryness. Extraction of the residue was carried out successively with anhydrous, 80 per cent, 50 per cent, and 25 per cent alcohol and finally with water. The insoluble residue was found to be chiefly inorganic.

The absolute alcohol extract was evaporated under reduced pressure. The residue from this evaporation was extracted with the same solvent, the 80 per cent alcohol extract being then added to the residue and evaporation carried out in the same flask. This residue was then extracted with 80 per cent alcohol, the next solution added to the residue and the same procedure followed for all the solutions in the order given above.

Table I shows the skin reactions to scratch tests given by ragweed pollen sensitive patients to these different fractions of both ragweed pollens. The Molisch reaction of the solutions is graded from + for a weak reaction to ++++ for a very strong reaction.

TABLE I

REACTIONS TO POLLEN CARBOHYDRATE FRACTIONS

SUCCESSIVE EXTRACTS	GIANT RAGWEED				SHORT RAGWEED			
	NO. PATIENTS		PER CENT POS.	MOLISCH TEST	NO. PATIENTS		PER CENT POS.	MOLISCH TEST
	POS.	NEG.			POS.	NEG.		
Anhydrous alcohol	1	9	10	++	0	9	0	++
80 per cent alcohol	5	5	50	++++	7	2	78	++++
50 per cent alcohol	9	1	90	++++	9	0	100	++++
25 per cent alcohol	3	6	33	+++	8	1	89	++++

As the fractions were not highly purified, the only conclusions we can draw from these results are (1) that there is a fairly close correlation between the skin-reacting activity of the solutions and their reactions to the Molisch test, and (2) that an alcohol concentration greater than 80 per cent should be used for precipitation of the active material.

Accordingly, preparations of purified polysaccharides were made by repeated precipitation from aqueous solution with ten volumes of absolute alcohol. The attempt to prepare material free from nitrogen was unsuccessful, although several methods were tried. The best preparations were made by a procedure similar to that used by Black,[2] which, however, in the case of the common ragweed, gives a product containing nearly 6 per cent nitrogen.

Very recently, Gough[4] has described a method of preparation of the timothy pollen polysaccharide which gave a product containing less

than 1 per cent nitrogen. He has not yet reported on the allergic activity of this material.

Preparation of Polysaccharides

The method of preparation used here for the polysaccharides which were tested pharmacologically and clinically was briefly as follows:

The aqueous pollen extract was evaporated to dryness, or almost to dryness, usually after coagulation of proteins by heat and acidification with acetic acid. The residue was extracted with 25 per cent alcohol or with distilled water. This solution after filtration was precipitated by addition of anhydrous alcohol until the total concentration was approximately 90 per cent. The precipitate was redissolved in distilled water or water containing a few drops of acetic acid, the solution filtered and reprecipitated. This process was repeated until at least five precipitations had been carried out on each sample. The final precipitate was washed with anhydrous alcohol and dried in air and over sulphuric acid. All evaporations were carried out under reduced pressure.

The material so purified gives a very strong Molisch test and does not reduce Fehling's solution before hydrolysis. The Millon and biuret reactions are negative. The nitrogen content of the polysaccharide from short ragweed pollen was 5.28 per cent and of that from the giant was 6.92 per cent. The polysaccharide prepared from timothy pollen contained only 3.68 per cent nitrogen.

Preparation of Proteins

The protein solutions were prepared by a method similar to that used by Stull, Cooke and Chobot[3] using repeated ammonium sulphate precipitations. After dialysis of the solutions, total solids were determined and the solution was diluted accordingly. For testing, sodium chloride or dextrose was added to make isotonic solutions. The dried carbohydrates were dissolved in a similar solution for comparison on a weight basis with the protein solution.

B. Pharmacological.

1. Intradermal comparisons on rabbits.

Rabbits were sensitized by intraperitoneal injections of whole pollen 1 per cent suspension. A few rabbits were likewise treated by injections of 1 per cent solution of the pollen polysaccharides. These animals gave very satisfactory skin reactions, but no conclusions may be drawn from this until we have more information regarding the nature of the nitrogen present in the polysaccharide preparation.

The animals were tested, after intravenous injection of trypan blue solution,[5] with serial dilutions of the solutions to be compared.[6] The dilutions as recorded are based upon the dry weight of protein or carbohydrate dissolved, or upon the weight of dry pollen extracted in the

case of whole pollen extracts. In Table II are shown the results of quantitative comparisons of pollen polysaccharides with whole pollen extracts and with pollen protein solutions upon rabbits sensitized either by polysaccharide solution or whole pollen suspension. The whole pollen suspensions and extract were prepared with equal weights of giant and short ragweed pollens. The table does not show complete protocols for each rabbit, but only the most dilute solution showing a definitely positive reaction. In most of the tests, dilutions were made so that each dilution gave a concentration one-tenth of that preceding.

TABLE II

COMPARISON OF POTENCY OF POLLEN POLYSACCHARIDES WITH WHOLE POLLEN EXTRACT AND POLLEN PROTEIN SOLUTION

RABBIT NO.	SENSITIZED BY	SOLUTION TESTED	WEIGHT REPRESENTED PER C.C. IN MOST DILUTE SOLUTIONS SHOWING POSITIVE REACTION ON (DATE)			
			3/30/32	4/15/32	5/11/32	7/13/32
550	C (7)	Ext.	10^{-4}	10^{-4}	--	--
		C (6)	--	--	10^{-5}	10^{-3}
		C (7)	10^{-4}	2.5×10^{-6}	--	--
		Protein	--	--	10^{-4}	10^{-4}
537	C (7)	Ext.	10^{-4}	10^{-4}	--	--
		C (6)	10^{-5}	--	--	10^{-6}
		C (7)	10^{-4}	10^{-4}	--	--
		Protein	--	--	--	10^{-6}
497	C (7)	Ext.	10^{-4}	00	--	--
		C (6)	10^{-5}	--	10^{-5}	--
		C (7)	10^{-6}	10^{-4}	--	--
		Protein	--	--	0	--
562	M. R. P.	Ext.	10^{-4}	10^{-4}	--	--
		C (6)	10^{-4}	--	--	10^{-5}
		C (7)	10^{-4}	2.5×10^{-6}	--	--
		Protein	--	--	--	10^{-4}
570	M. R. P.	Ext.	10^{-3}	00	--	--
		C (6)	--	--	00	00
		C (7)	00	00	--	--
		Protein	--	--	0	0
557	M. R. P.	Ext.	10^{-5}	10^{-4}	--	--
		C (6)	--	--	--	--
		C (7)	10^{-6}	2.5×10^{-6}	--	--
		Protein	--	--	--	--
561	M. R. P.	Ext.	10^{-5}	0	--	--
		C (6)	10^{-6}	--	10^{-6}	--
		C (7)	10^{-3}	0	--	--
		Protein	--	--	10^{-6}	--
575	M. R. P.	Ext.	00	10^{-3}	--	--
		C (6)	00	00	10^{-4}	10^{-3}
		C (7)	00	00	--	--
		Protein	--	--	10^{-4}	0
493	Control	C (7)	00			

M.R.P. Mixed ragweed pollen (50 per cent short and 50 per cent giant) suspension.
Ext. Mixed ragweed pollen extract.
C(6). Giant ragweed pollen polysaccharide.
C(7). Short ragweed pollen polysaccharide.
Protein. Giant ragweed pollen protein.
-- Not tested.
0 No reaction to solution representing 10^{-4} gm. per c.c.
00 No reaction to solution representing 10^{-3} gm. per c.c.

The tests on 4-15-32, however, used dilutions representing 5×10^{-6} and 2.5×10^{-6} grams per c.c. in addition to the decimal dilutions ordinarily used.

It can readily be seen that the skin tests on rabbits show no constant difference in activity between the polysaccharides and the whole pollen extract or the protein when diluted on a weight basis.

2. Precipitin tests.

Rabbits which had been intensively immunized against giant ragweed, short ragweed, timothy and orchard grass pollens (five animals being used for each pollen) were tested for the presence of precipitins. The blood for precipitin tests was drawn in the morning, and the animals were skin tested in the afternoon of the same day to establish their sensitivity. The ring test was used to demonstrate the presence of precipitins, the pollen extract being layered over the serum.

Using a 1:200 whole pollen extract, the presence of precipitins was demonstrated in the serum of four timothy, four orchard grass, four short ragweed, and four giant ragweed sensitive animals. One of the orchard grass sensitive rabbits had died, and the other three which failed to show precipitins all gave definite skin reactions. Four of the animals showing precipitins failed to give well-defined skin reactions.

Each of the serums from the grass pollen sensitized rabbits was tested for precipitins against a 1 per cent solution of timothy pollen polysaccharide. No precipitation occurred in any instance. The best ragweed pollen precipitating serum was used to test for precipitation with polysaccharides from short and giant ragweed, 1 per cent solutions. Again no precipitins for the polysaccharide fractions could be demonstrated.

The best precipitating serums for each pollen were pooled and used for testing solutions of purified proteins. These protein solutions were quite dilute, that from timothy pollen containing total solids 4.4 grams in 10,000 c.c. and from giant ragweed pollen 2.6 grams in 10,000 c.c. They were the same preparations used in some of the skin testing. Precipitation occurred in the tube containing giant ragweed pollen protein and the homologous serum, but not in the others. This failure to demonstrate precipitins against the other pollen protein is probably due to the relatively high dilutions used. The precipitin titer of the serum of pollen sensitized rabbits is never very high.

3. Desensitization experiments.

Ragweed pollen sensitized rabbits were given intravenous injections of 5 c.c. of the homologous pollen protein solution in the morning, and were then skin tested with serial dilutions of both protein and polysaccharide solutions. The short ragweed pollen protein solution had a concentration of 1.38 gram in 1,000 c.c. and that from giant ragweed 1.26 gram in 1,000 c.c. on the basis of total solids in the purified

solution. The corresponding polysaccharide solutions were prepared by weighing out the requisite amount of the dried material to give the same concentration. For skin testing, each dilution represented one-fourth the concentration of that preceding. Dilutions were used up to 1.26 or 1.38 grams in 256,000 c.c. but as no higher dilutions than 1.26 gram in 4,000 c.c. reacted, they are not shown in Table III.

TABLE III

SKIN TESTS UPON RABBITS DESENSITIZED BY PROTEIN SOLUTION

RABBIT NO.		68	23	8			60	32	1	17
Short carbohydrate	1.38:1000	0	0	0	Giant carbohydrate	1.26:1000	tr.	0	0	0
	1.38:4000	0	0	0		1.26:4000	0	0	0	0
Short protein	1.38:1000	0	+	+	Giant protein	1.26:1000	2+	tr.	0	0
	1.38:4000	0	0	0		1.26:4000	+	0	0	0

It thus appears that after attempted desensitization by means of intravenous injection of the purified protein solution, which responded negatively to the Molisch test, in no case was a greater reaction obtained from the polysaccharide than from the protein solution in corresponding concentration. With the exception of No. 60, all these animals had responded to higher dilutions on the previous skin test.

C. Clinical.

1. Direct tests upon hay fever patients.

During the summer of 1931, ragweed sensitive patients in the Asthma and Hay-Fever Clinic at Northwestern University Medical School were tested with 1:100 solutions of giant and short ragweed pollen polysaccharides, using the scratch method, with the following results:

	Positive	*Negative*	*Per Cent Positive*
Carbohydrate from giant ragweed pollen	14	8	64
Carbohydrate from short ragweed pollen	14	6	70

While scratch tests are valuable in indicating the allergic activity of solutions, intradermal tests are usually conceded to be more reliable. They have been found to be useful for quantitative comparison of two solutions if these are used on the same individual and a sufficient number of dilutions are used to establish the point at which a reaction fails to be elicited.[7] By this means in 1932 the relative potency of the carbohydrate preparations and that of whole pollen extracts were compared, using as a basis the weight of dry pollen extracted or of dry polysaccharide dissolved.

Five patients were used for comparison of short ragweed pollen polysaccharide with ragweed pollen extract. Four of these showed a reaction to the whole pollen extract in higher dilution than to the polysaccharide solution, while the fifth showed the two nearly equal. Three other patients were used for comparison of giant ragweed pollen

carbohydrate, prepared by nitrous acid treatment, with whole ragweed pollen extract. Again the whole pollen extract proved equal or greater in potency.

Giant ragweed pollen protein and carbohydrate solutions were compared on seventeen patients. In only one test the polysaccharide appeared more potent, while the protein showed greater potency in twelve, and the two solutions were approximately equal in four patients.

2. Passive transfer tests.

Serums from three ragweed sensitive patients were used for testing. Passive transfer sites with these were prepared on six normal individuals. Half the sites were then tested and finally desensitized with carbohydrate solution and half with protein solution, using equivalent concentrations by weight, as was done in the pharmacologic work. The sites after exhaustion to one were then tested with the other. In no case did a definite reaction occur with the polysaccharide in sites desensitized to the homologous protein; while a pronounced reaction always resulted when protein solution was injected into sites completely desensitized to the polysaccharide solution.

DISCUSSION

The earlier results seemed to substantiate the work of Black[2] on the reactivity of pollen polysaccharides. The polysaccharide preparations, which did not give the ordinary protein reactions but contained a high percentage of nitrogen, gave skin reactions on sensitive individuals or sensitized rabbits in high dilution. However, protein tests are not particularly sensitive, even in comparison with many other chemical tests. And all chemical tests appear woefully inadequate when we consider the extreme delicacy of biologic reactions. Dilutions of one to ten million on the dry weight basis on many patients, give a pronounced skin reaction. Assuming a value of 0.1 mg. nitrogen per c.c. in a 1:100 pollen extract, or 6 per cent nitrogen in the dry polysaccharide, a $1:10^7$ dilution of pollen extract would contain approximately 10^{-6} mg. or 10^{-9} gm. nitrogen per c.c.; while a similar dilution of polysaccharide would contain 6×10^{-6} mg. nitrogen per c.c. The protein fraction prepared by Stull, Cooke, and Chobot[3] from ragweed pollen contained 12.59 per cent nitrogen. On this basis, the nitrogen in a $1:10^7$ protein solution would equal 1.26×10^{-5} mg. per c.c. The nitrogen ratio in corresponding dilutions is then approximately

$$\text{Pollen extract: Polysaccharide: Protein} = 1:6:12.$$

At least half the nitrogen in the extract is nonprotein, and nothing is yet known of the nature of that in the polysaccharide. Since reactions are elicited by such high dilutions, chemical tests cannot be relied upon to furnish evidence as to the nature of the active substance. The results of intradermal comparisons of solutions thus do

not enable us to draw any definite conclusions, although in the tests on patients the protein appears somewhat more active than the others.

The desensitization tests on rabbits tend to confirm the theory that the specifically active substance in pollen extracts is the protein. The polysaccharide fraction gave no evidence of containing an antigen immunologically distinct from the protein fraction. It is likewise significant, in view of the behavior of bacterial polysaccharides which exhibit specific properties, that rabbit serum containing precipitins for whole pollen extract fails to precipitate a 1 per cent solution of the polysaccharide. The protein solutions tested were much more dilute, but with one of these precipitation occurred with the corresponding immune serum.

Passive transfer tests with the serum of ragweed pollen sensitive patients furnish the most conclusive evidence so far obtained regarding the nature of the allergen. Sites desensitized to the protein solution in no case gave a further reaction when tested with the polysaccharide solution. This agrees with the results of Stull, Cooke and Chobot[3] on a larger number of serums. If it is admitted that the reagins in the serum parallel the clinical sensitivity of patients, possibly the only weakness in this evidence is the fact that hay fever patients vary so greatly in their reactions that some individuals may yet be found not to fall into line with the limited series so far observed. The work is being further extended to include the study of more pollens and a greater number of patients. Other methods of preparation of the polysaccharide are being used to remove any protein nitrogen present.

SUMMARY

Protein and polysaccharide fractions of pollens have been prepared and studied with the view of determining their relative importance as allergens. The preparation of nitrogen-free pollen polysaccharides has not yet been successful.

Comparative skin tests upon sensitized rabbits or upon hay fever patients gave no conclusive evidence of difference in activity of the two fractions from ragweed pollens.

Precipitin tests with immune rabbit serum which precipitated with 1:200 whole pollen extracts failed to show any precipitins for the polysaccharide fractions of ragweed or grass pollens; while precipitation occurred with a much more dilute solution of giant ragweed pollen protein.

Rabbits skin tested soon after an intravenous injection of ragweed pollen protein showed less reaction to the homologous polysaccharide than to the protein solution.

Passive transfer tests with the serum of ragweed sensitive patients were carried out. Passively sensitized sites failed to react to the polysaccharide solution after desensitization to the homologous protein.

On the contrary, sites desensitized to polysaccharides gave 100 per cent positive reactions to the homologous protein.

All the evidence points toward the conclusion that the allergen in ragweed and grass pollens is protein in nature and that the polysaccharide fraction plays no part in the specific activity.

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CONSTITUTION AND ALLERGIC MANIFESTATIONS*†

I. Age-Sex Incidence of Allergic Conditions

Preliminary Report

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SINCE time immemorial men have sought a relationship between constitution and disease. Of recent years the interest in the subject has been renewed, particularly by the pathologists and the internists. It is now thought that some of our problems of immunity may have their solution in the recognition of various constitutions. Petersen[1] defines the term "constitution" as embracing "not only the quality of protoplasm in its form and structure, but the functional status as made apparent in physiological and pathological reactivity—in adaptability to change in environment—in modifications produced by season, climate, diet, age, endogenous and exogenous irritants, disease, physical and mental trauma, and the ever varying forces of the universe of which the individual is a part."

The study of constitution in its relationship to allergic manifestations has been undertaken as one of our major problems, and I present a preliminary report on one phase of this subject; the age-sex incidence in 1,786 allergic individuals, where careful histories were obtainable.

OBSERVATIONS

The cases were classed into three main groups: (1) hay fever, (2) asthma, and (3) allergic dermatosis. They were further grouped by sexes into five-year periods according to the onset of allergic manifestations. Our findings are given in Tables I, II, and III, and graphically shown in Figs. 1, 2, and 3.

In the three groups studied, it will be observed that males predominate in the proportion of two to one in the first decade of life. With the onset of puberty, the proportion is reversed and females predominate in the ratio of five to three. The greatest period of increase is in the second decade, during the years of physiologic adjustment in the female. From the middle of the third decade and on, the sex incidence is fairly equal, and grades off fairly evenly.

When we study the three groups as to sex incidence (Table IV), we find that males predominate in a ratio of 55 to 45 in the hay fever and asthma groups, but in the allergic dermatosis group females predomi-

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†Read at the Eleventh Annual Meeting of the Association for the Study of Allergy, Milwaukee, Wis., June 12 and 13, 1933.

TABLE I

INCIDENCE OF HAY FEVER IN 856 CASES

YEAR	FEMALE		MALE	
	NO.	%	NO.	%
0-5	35	8.88	75	16.23
6-10	51	12.94	94	20.34
11-15	44	11.16	48	10.38
16-20	73	16.23	33	7.14
21-25	62	15.73	48	10.38
26-30	44	11.16	61	13.20
31-35	44	11.16	40	8.87
36-40	27	6.85	31	6.71
41-45	10	2.53	12	2.54
46-50	4	1.01	11	2.33
51-55	—	—	5	1.06
56-60	—	—	3	0.64
61-65	—	—	—	—
66-70	—	—	1	0.21

Percentages are of the total of each sex.

TABLE II

INCIDENCE OF ASTHMA IN 743 CASES

YEAR	FEMALE		MALE	
	NO.	%	NO.	%
0-5	43	13.07	97	23.40
6-10	35	10.63	38	8.91
11-15	19	5.77	25	6.04
16-20	45	13.67	28	6.73
21-25	35	10.63	28	6.73
26-30	31	9.42	32	7.46
31-35	34	10.33	33	7.70
36-40	33	10.03	37	8.69
41-45	24	7.26	36	8.43
45-50	16	4.86	36	8.43
51-55	7	2.12	14	3.38
56-60	4	1.21	4	0.94
61-65	1	0.30	6	1.42
66-70	2	0.60	—	—

Percentages are of the total of each sex.

TABLE III

INCIDENCE OF ALLERGIC DERMATOSIS IN 187 CASES

YEAR	FEMALE		MALE	
	NO.	%	NO.	%
0-5	29	24.78	39	55.71
6-10	9	7.68	2	2.85
11-15	9	7.68	1	1.42
16-20	19	16.06	4	5.70
21-25	14	11.96	4	5.70
26-30	6	5.12	4	5.70
31-35	8	6.84	6	8.55
36-40	6	5.12	3	4.27
41-45	6	5.12	5	7.12
46-50	10	8.54	2	2.85
51-55	1	0.85	—	—

Percentages are of the total of each sex.

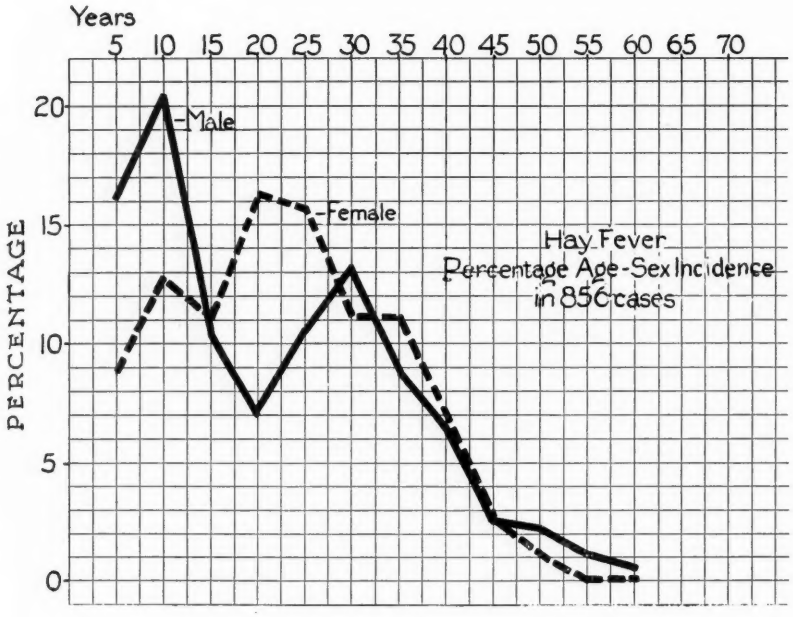
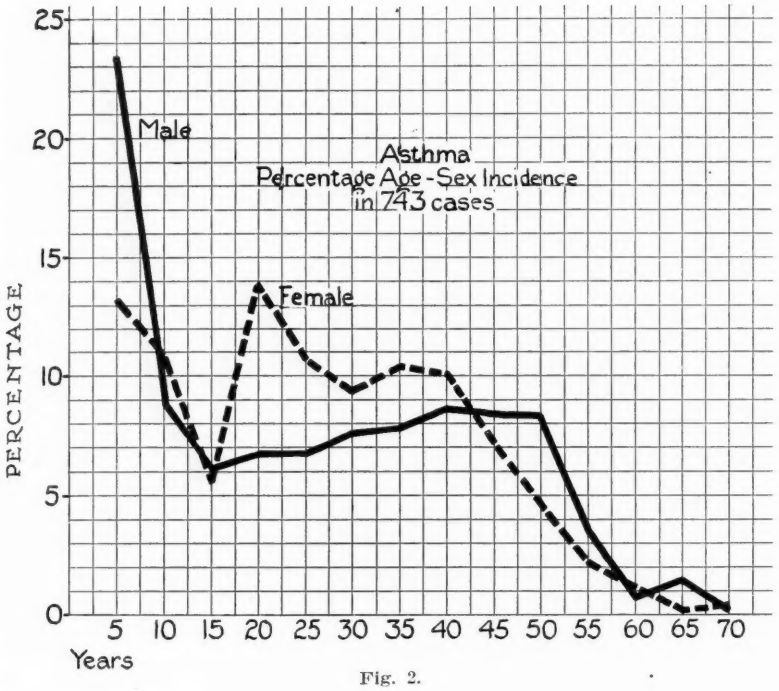

Years
5 10 15 20 25 30 35 40 45 50 55 60 65 70
20
15
10
5
0
PERCENTAGE
Male
Female
Hay Fever
Percentage Age-Sex Incidence
in 856 cases

Fig. 1.


25
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PERCENTAGE
Male
Asthma
Percentage Age-Sex Incidence
in 743 cases
Female
5 10 15 20 25 30 35 40 45 50 55 60 65 70
Years

Fig. 2.

nate in a ratio of 63 to 37. This latter ratio may be accounted for in part by the presumption that males may not present themselves for skin conditions as frequently as do females.

In studying the incidence in the first decade of life as a group, we

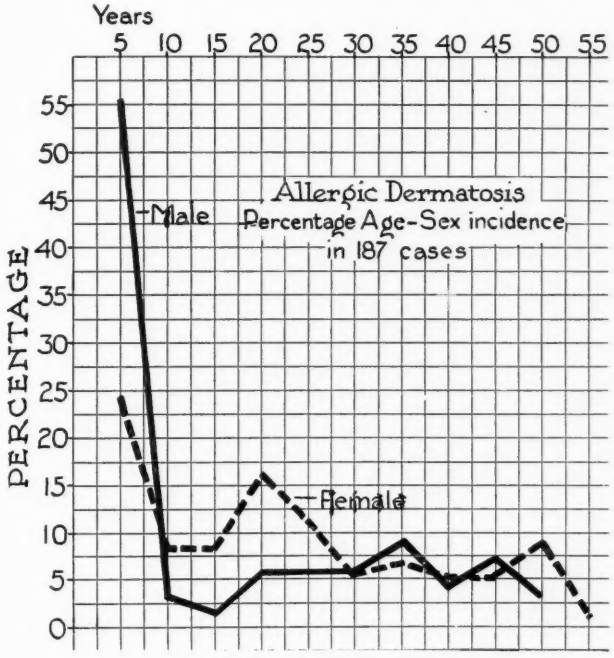

Fig. 3.

find that the incidence in percentage of the total for the decade in either sex is parallel in each of the three groups. (Tables V, VI, and Fig. 4.) It is interesting to note the high incidence in both sexes of the allergic dermatosis in the first year of life and the marked drop

TABLE IV

SEX INCIDENCE IN 1786 CASES OF ALLERGY

	TOTAL	FEMALE		MALE	
		NO.	%	NO.	%
Hay fever	856	394	46.01	462	53.92
Asthma	743	329	44.28	414	55.72
Allergic dermatosis	187	117	62.57	70	37.43
Total	1786	840	50.95	946	49.05

in the second year. When we compare the asthma group in the first decade with those described by Bullen,[2] Peshkin,[3] Coke,[4] and Bray,[5] we find as great a variation in any year group as do these authors (Table VII).

The association of other allergic manifestations in the hay fever group is of interest in their relationship to the age-sex incidence as pointed out above. Asthma either seasonal or perennial was found in 39.11 per cent of all hay fever cases, and all other allergies including asthma

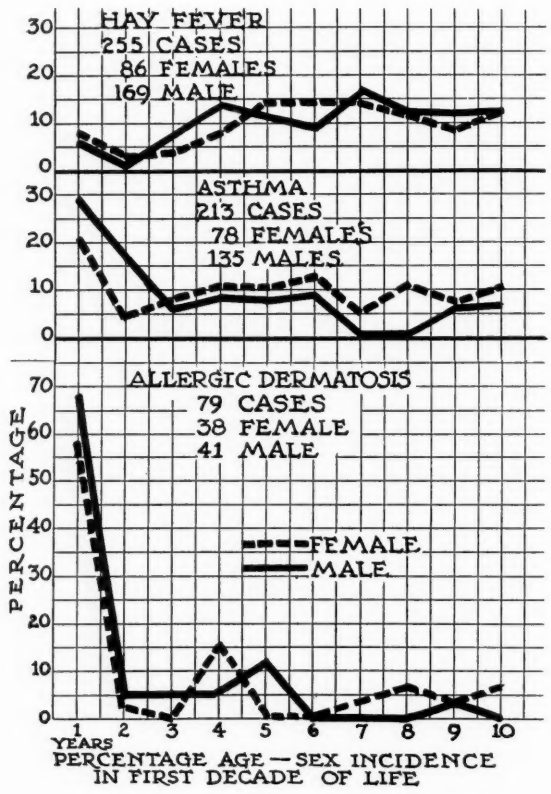

Fig. 4.

TABLE V

SEX INCIDENCE IN PERCENTAGE OF HAY FEVER, ASTHMA AND ALLERGIC DERMATOSIS IN FIRST DECADE

	FEMALE			MALE		
NO. CASES / YEAR	H. F. 86	ASTH. 78	A. D. 38	H. F. 169	ASTH. 135	A. D. 41
0-1	7.8	20.6	58.6	5.5	28.8	67.6
1-2	3.2	4.4	3.1	1.5	16.1	5.8
2-3	4.7	7.3	—	7.0	5.9	5.8
3-4	7.8	10.3	15.5	13.6	9.1	5.8
4-5	14.3	10.3	—	11.8	8.4	11.7
5-6	14.3	13.2	—	9.4	9.1	—
6-7	14.3	5.8	3.1	16.5	1.4	—
7-8	11.1	10.3	6.2	11.8	1.4	—
8-9	9.5	7.3	3.1	11.8	5.9	2.9
9-10	12.6	10.3	6.2	11.8	6.6	—

Percentages for each condition are based on the ten-year totals for each sex.

TABLE VI

TOTAL PERCENTAGES OF INCIDENCE IN FIRST DECADE

NO. CASES YEAR	HAY FEVER 255	ASTHMA 213	ALLERGIC DERMATOSIS 79
0-1	6.3	25.9	64.5
1-2	2.1	11.3	5.3
2-3	6.3	6.5	3.5
3-4	11.0	10.3	12.4
4-5	12.6	9.2	7.1
5-6	11.0	11.3	—
6-7	15.8	4.3	1.8
7-8	11.6	5.9	3.5
8-9	11.0	6.5	1.8
9-10	12.1	8.6	3.5

TABLE VII

AGE INCIDENCE OF ASTHMA IN FIRST DECADE IN PERCENTAGE

AUTHOR	CASES	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10
Bullen	197	13½	10	17½	13	9½	11	5½	9½	6	3
Peshkin	100	10	21	18	18	9	9	4	3	7	1
Coke	135	29	14	7	9	17	8	7	3	2	3
Bray	200	22	18½	14	13	12	8½	5½	3	1½	1
Nelson	213	18½	15¾	14	13	12	9	5½	4¾	4	2

were found in 46.20 per cent of cases, 53.33 per cent in males and 46.67 per cent in females. This parallels the sex incidence of hay fever.

DISCUSSION

The relationship between sex distribution and age of onset of allergies is not a new finding. It has been referred to by such authors as Adam,[6] Berkart,[7] Bray,[5] Coke,[4] Hermann,[8] Peshkin,[3] and Salter,[9] but most reports have been on smaller groups than the one here submitted, and have been from other localities. Walzer[10] states that "sex plays an insignificant rôle as an etiological factor in asthma." As far as percentage of the total, yes, and this is in accord with the observations of Rackemann[11] and Walker,[12] but I believe it may play an important rôle in the first two decades of life. The predominance of the male in the first decade is found in a few other conditions, as pyloric stenosis, tetany, and laryngismus stridulus. I shall make no attempt to explain the incidence as shown, this work being in its infancy. Work is now under way in an attempt to explain the high incidence of males in the first decade of life.

CONCLUSIONS

1. A preponderance of males was demonstrated in the first decade of life in groups of hay fever, asthma and allergic dermatosis.

2. A preponderance of females was demonstrated in the second and third decades in groups of hay fever, asthma and allergic dermatosis.

3. In the first decade, when considered as a group, the incidence in percentage of the total for the group in either sex is parallel for each condition.

4. The occurrence of other allergic manifestations in association with hay fever was found to be in the same proportion in either sex as the incidence of hay fever in the sexes.

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SKIN REACTIONS TO TOBACCO ANTIGEN IN SMOKERS AND NONSMOKERS*

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OBSERVATIONS on the occurrence of positive skin reactions to various tobacco antigens in patients suffering from thromboangiitis obliterans (Buerger's disease) were recently reported by Harkavy, Hebald and Silbert.[1] They were subsequently confirmed by Sulzberger.[2] Our first report was based on the results in 68 cases of thromboangiitis obliterans and 122 controls. The second[3] dealt with 87 cases of thromboangiitis, of which 76 patients or 87 per cent were found to be sensitive to tobacco; 262 male control cigarette smokers, of whom 43 or 16 per cent reacted to tobacco extracts, and 43 women mostly nonsmokers of whom only three reacted, who had allergic stigmata. Sulzberger's figures were 77 per cent positive reactions in the cases with thromboangiitis obliterans and 36 per cent for the controls.

The present communication, read in part before the Society for the Study of Asthma and Allied Conditions (May, 1933), is based on a total of 103 cases of thromboangiitis obliterans and an additional group of 57 male control smokers making a grand total of 319 male controls, and 126 female nonsmokers.

The results of the skin reactions to tobacco in 103 cases of thromboangiitis obliterans are in substantial agreement with those previously reported. Eighty-nine patients or 86+ per cent of cases gave positive reactions to tobacco. On the other hand the percentage of the positive reactions observed among the 319 control smokers is somewhat larger than among the 262 reported previously, 65+ positively reacting individuals were encountered, an incidence of 20+ per cent.

The tobacco employed in this investigation consisted of the uncured leaf of Burley, Maryland, Virginia and Xanthis (Turkish). Separate extracts of these were made according to the method of Coca. A tobacco extract representing a mixture of various tobaccos which we obtained from the Allergy Department of the New York Hospital through the courtesy of Dr. Cooke was also used. This extract was labelled "Coca" and gave us the largest number of positive reactions. It was prepared according to Dr. Coca in such a manner as to make it as nicotine free as possible. "The tobacco is first extracted with a mixture of alcohol and ether which removes most of the nicotine and undesirable coloring matter. This is then dialized for a considerable time against extracting fluid of 'Coca.'"

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Every case of thromboangiitis obliterans and every control was tested intracutaneously with 0.01 c.c. of each of the five different tobaccos and the reactions were read within fifteen to twenty minutes. All the extracts were diluted 1:10 because the original solution was irritating and produced false positives. Every patient and every control was also tested with 0.01 c.c. of 0.01 solution of ragweed and Coca's extracting fluid. The ragweed was important because it enabled us to pick up latent hay fever patients and to obtain a clue as to the family history of allergy. In this respect we found it one of the most reliable of control antigens, in contrast to extracts such as feathers or dust, which when injected intradermally induced (nonspecific?) wheals and erythema differing in intensity in almost 90 per cent of normal controls as well as atopic individuals.

Control Smokers.—In testing the control smokers for tobacco especial care was used to exclude atopic individuals with frank asthma or hay fever. This precaution was justified by the experience that varying degrees of positive skin reactions to tobacco antigen were observed in every one of 15 patients with ragweed hay fever. These reactions may be evidence of multiple sensitization characteristic of the atopic state. In this connection it is important to report that out of 103 cases of thromboangiitis obliterans only five were found to be sensitive to ragweed by intradermal skin tests.

The 319 control smokers consisted of 47 normal college students, between the ages of sixteen and twenty-one years; 292 adults, mostly Russian Jews, between the ages of twenty-six and sixty-eight years, 108 of whom suffered from various ailments, arterial hypertension, nephrolithiasis, carcinoma of stomach, bronchiectasis and pulmonary neoplasm, 28 had arteriosclerotic circulatory disturbances of the extremities, 5 infectious asthma, 60 ulcer of the stomach and duodenum,[3] 71 coronary artery disease.[4]

Sixty-five of this series of 319 controls or 20.4 per cent gave positive skin reactions to tobacco.

Analysis of the 65 smokers who reacted positively to tobacco disclosed that they fell into two categories. Forty-seven cases were patients with the symptom complex of angina pectoris presenting evidence of coronary artery disease or patients with gastroduodenal ulcer. Only 18 consisted of normal individuals or those with miscellaneous ailments.

Seventy-one males with coronary artery disease, presenting the syndrome of angina pectoris, were tested. All were smokers and 31, or 43 per cent, reacted to tobacco. Ten of these, almost a third, gave a personal or family history of asthma and hay fever. This incidence of atopy is certainly three times as large as the estimated 7 to 10 per cent[5, 6] for the general population. The information as to allergy was elicited on special inquiry, only after the positive reactions to tobacco

had been obtained. In spite of the primary vascular nature of coronary artery disease, the possible significance of allergic factors has thus far been neglected. Yet there is a vascular element in the phenomena associated with asthma, hay fever and other manifestations of hypersensitiveness to protein.

Sixty cases of gastric and duodenal ulcer were tested and 16 (or 26 per cent) reacted to tobacco. Eleven (or 18 per cent) were also sensitive to pollens and gave a history of asthma and hay fever. This group of cases is still under investigation.

The remaining control smokers whose skin was sensitive to tobacco constitute 5 per cent of the total series. No history of atopy or reactions to pollen were obtained in any of them. In this group of controls the reactions were usually one-plus. A one-plus reaction with the tobacco antigens employed was characterized by a wheal of about 5 to 6 mm. in diameter and a zone of erythema averaging 2 to 2.5 cm. in diameter. Occasionally a two-plus reaction was seen; whereas in the first category of coronary and ulcer cases, two-plus, three-plus and even four-plus reactions were not uncommon.

Control Nonsmokers.—In nonsmokers the only contact with tobacco was its presence in the atmosphere or through the use of insecticides.

One hundred and twenty-six women varying between the ages of twenty and sixty years were examined. They consisted of 20 healthy adults and 83 suffering from miscellaneous disorders usually seen in the average hospital population, i.e., arterial hypertension and cardiac

TABLE I

TOBACCO REACTIONS IN FEMALE CONTROLS. NONSMOKERS

AGE		DIAGNOSIS	BURLEY	COCA	MARYLAND	VIRGINIA	XANTHIS	RAGWEED 0.01	BIRCH
61	S. O.	Coronary artery disease	+++	+	+++	+++	+++	+	
64	B. C.	Coronary artery disease	±	+					
43	F. N.	Coronary artery disease (Father asthma, sister hay fever)	+	++		++	++		
50	S. B.	Postoper. appendectomy	+	+	+	+	+	+	
40	M. S.	Arthritis				+		++	
25	C. H.	Fistula in ano.	±	±	±	±	±	±	
17	S. C.	T. B. adenitis (hay fever)	+++	+		+	+	+	++
22	H. B.	Observation	±	±	±	±			
51	B. W.	Observation				+			
32	S. K.	Curettage					±		
26	B. B.	Plastic operation		+		+	+		
20	D. M.	Submaxillary cyst	+	+	+	+	+		
51	B. J.	Cardiac neurosis	+	+			+		
28	A. S.	Neoplasm of spinal cord	+	++			+		
34	J. B.	Gastric neurosis		+					
37	E. M.	Ulcer of stomach? (Father asthma)		±					

diseases of various types, pulmonary and gastric neoplasms, bronchiectasis, diabetes, etc. Many of the patients examined were bedridden, some convalescing. All were afebrile. Patients with acute inflammatory processes or skin eruptions were not included.

The results were as follows:

Of the 126 adult nonsmoking females tested, 16 reacted to tobacco (12 per cent). Five of these also reacted to ragweed pollen and one to birch. One of them gave a history of spring hay fever, and the other had a father who had asthma and a sister who suffered from hay fever.

SUMMARY

1. *Nonsmokers, Female.*—One hundred and twenty-six adult nonsmoking women were tested with five different tobacco antigens: Burley, Coca, Maryland, Virginia, and Xanthis (Turkish). Sixteen, or 12 per cent, were found to give positive skin reactions. Five of the sixteen reacted also to ragweed antigen, and two of the five according to their histories were constitutionally allergic. Eleven of the sixteen, or 9.2 per cent, gave only one-plus or plus minus reactions to tobacco.

2. *Smokers, Male.*—Of 319 male smokers excluding individuals suffering with thromboangiitis obliterans 65, or 20 per cent, reacted to tobacco.

3. Of the 65 control smokers who reacted to tobacco 18 were normal individuals or patients suffering from miscellaneous disorders. Thirty-one were individuals with coronary artery disease presenting symptoms of angina pectoris. Sixteen were cases with gastric or duodenal ulcer. The incidence of positive skin reactions to tobacco in patients with coronary artery disease or gastroduodenal ulcer is definitely larger than that among normal people or control patients with other diseases.

4. Out of the 103 cases with thromboangiitis obliterans, 89, or 86 per cent, reacted to tobacco.

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AN EVALUATION OF SKIN REACTIONS IN FOOD SENSITIVE PATIENTS*

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CERTAIN allergists hold that many foods productive of clinical sensitizations cannot be satisfactorily indicated by scratch or intradermal skin testing. It is also recognized that food reactions often occur in patients who have no allergic symptoms from such foods. Because of this possible fallibility of skin testing in demonstrating clinical food allergies, various methods of diet trial have been recommended as aids to diagnosis, among which is that which I suggested in 1928[1] which utilizes my so-called "elimination diets."

I have not been alone in my position that food allergy cannot always be demonstrated by skin reactions. Thus Schloss[2] originally stressed this difficulty, and since then Blackfan,[3] O'Keefe,[4] Duke,[5] Brown,[6] Rackemann,[7] Andresen,[8] Eyermann,[9] Vaughan,[10] Hill,[11] Phillips,[12] Coca, Walzer and Thommen,[13] Hopkins and many others have reported negative tests to allergy-producing foods. Vaughan[10] has discussed negative food reactions and has suggested modifications of the "elimination diets" based on the biologic relationship of foods. Rackemann concludes, "Despite a negative skin test, specific food sensitiveness may exist." Gay[15] says that skin reactions to foods are notoriously inaccurate in 50 per cent of all patients. Alexander[16] especially has emphasized the negative test and has stated that 50 per cent of the foods productive of allergy give negative reactions, which estimate is probably a liberal one in adults.

This emphasis of the negative reaction to food allergens is not to be construed to mean that food reactions are not obtained by scratch or intradermal testing. Most allergic patients tested give varying numbers of scratch or intradermal reactions to foods or condiments, but such patients frequently fail to react to all allergy-producing foods. Such positive reactions are especially frequent in childhood and occur in all ages throughout life. They must always be checked, however, by diet trial to determine their clinical significance. Thus, the importance of careful skin testing by the scratch supplemented by the intradermal tests is evident and I have always emphasized that the "elimination diets" should be modified by positive skin reactions or by definite histories of food disagreements.

*Read at the Eleventh Annual Meeting of the Association for the Study of Allergy, Milwaukee, Wis., June 12, and 13, 1933.

The occurrence of the negative skin reaction and of the false positive reaction has been most inconvenient, necessitating as it does the frequent use of trial diets to work out effectually problems due to food allergies. Without the use of trial diets many manifestations of food allergy are likely to be unrecognized by the physician. For several years, I have tried various food extracts by the scratch and intradermal methods with the hope that the clinical food allergies may be more successfully determined. Some of the studies which have been made on the evaluation of food reactions in patients negative to the scratch tests to foods to which clinical sensitizations have been demonstrated will be presented in this article. This discussion is of special importance in view of the increasing number of commercial food allergens which are being offered the medical profession with the assurance that with their use specific food sensitizations can be determined.

INVESTIGATIONS

Studies on the dependability of the intradermal reaction in the determination of known food sensitizations were made with commercial extracts obtained from three different companies. For this purpose 14 patients were chosen who have been under observation for one to two years and whose symptoms have been proved to be due to specific foods. All had given negative scratch reactions to the dried food allergens of Company I which had been found active and productive of good positive scratch tests in certain patients clinically sensitive to most of the respective foods. Many other patients who gave negative scratch reactions to foods causing clinical symptoms over a period of years have been tested intradermally with different food extracts prepared by private and commercial laboratories with the same essential results as those which follow.

These 14 patients were selected in part to illustrate the different manifestations of food allergy. Thus, patients suffering with bronchial asthma, bronchitis, perennial hay fever, migraine, allergic toxemia, angioneurotic edema, gastrointestinal allergy, allergic dermatosis, and arthritic pains were studied. The symptoms in these patients were relieved and reproduced on different occasions by the specific elimination and addition of these foods and not merely by the change in diet, and in each case the possibility of food allergy as a cause of the recorded symptoms was assured.

For comparative purposes only 20 important representative foods were chosen, and the 14 patients were tested intradermally with two commercial preparations of all such foods, and all but three patients were tested with wheat, egg and milk extracts obtained from a third firm. The first product was a 1:200 dilution of a 2 per cent extract

TABLE I

INTRADERMAL SKIN REACTIONS IN PATIENTS CLINICALLY SENSITIVE TO KNOWN FOODS

	CASE 1			CASE 2			CASE 3			CASE 4			CASE 5			CASE 6			CASE 7		
	A.H.-M.-F.-60			H.W.-M-13			G.B.M-M-47			J.R.M-F-34			M.D.-S-F-32			A.A.-M-M-41			G.V.-M-M-48		
	GASTROINTEST. ALLERGY			BRONCHIAL ASTHMA			MIGRAINE			BRONCHIAL ASTHMA			G.I. ALLERGY TOXEMIA, FACIAL ERUPTION			ANGIONEUROTIC EDEMA			ARTHRITIC PAINS HEADACHES BRONCHITIS		
	CLIN. SENS.	PRODUCTS I	PRODUCTS II	CLIN. SENS.	PRODUCTS I	PRODUCTS II	CLIN. SENS.	PRODUCTS I	PRODUCTS II	CLIN. SENS.	PRODUCTS I	PRODUCTS II	CLIN. SENS.	PRODUCTS I	PRODUCTS II	CLIN. SENS.	PRODUCTS I	PRODUCTS II	CLIN. SENS.	PRODUCTS I	PRODUCTS II
1 Wheat	+		+	+			+	+				√ ①	+		± ①	+		+ ①	+		①
2 Egg	+			+			?		√		±	①		±	①	+		①	+	·	①
3 Milk	+			+	++	+				+		①	+	√	①	+		①	+		①
4 Corn			±√			+	+					√	+		+√ √				+		√
5 Rice		±	±√			++	+		+√	+		++√ √	+		+√ √ √			+			++
6 Rye			+	+	+	±	+		+√			±√	+		+			++	+		√
7 Chicken									√ √ √					√	√				+		
8 Lamb		+						+													
9 Beef								±			+			±	√				+		
10 Carrot					+			+	√ √		++++			√	+√					±	√
11 Pea									++√			++			+			+	+		+
12 Tomato	+											+			±√						
13 Spinach			+√ √						√									±			√
14 String bean		√						±	+√ √			+		+√	±√ √			+			+
15 White potato			√ √						√ √ √						+				+	√ √	
16 Lemon						√		++	+				+	√					+	+	+
17 Grapefruit			+					±					+	+	++√ √				+		
18 Pineapple			+√						++√			++	+	+√	+					±	
19 Pear			+									±√	+	√ √ √	++√ √			±	+		
20 Apple		+	√ √				?		++√ √			±√	?	√	++√ √			+	+		√

Key: +, ++, +++, ++++ (Varying degrees of positive immediate reactions).
± (Questionable immediate reactions).
√, √ √, √ √ √ (Varying degrees of delayed reactions).

① Intradermal tests with extracts from Company III were negative.

Can take: Rice, lamb, carrot, spinach, beet, string bean, tomato, peach, pineapple, sugar, olive oil. (Case 7.)

NOTE: One-plus reactions indicate a slightly irregular wheal larger than the control or one with definite erythema as compared with the control. Two-plus and three-plus reactions indicate corresponding increases in these findings. Immediate reactions were read in from 20 to 30 minutes and delayed reactions in 6 hours and in 18 to 24 hours. Blank spaces indicate negative reactions.

(in 46 per cent glycerin and 10 per cent saline solution) of the dry powdered allergen of Company I. This 2 per cent extract had been sterilized by Berkefeld filtration. The second products were kindly

TABLE I—CONT'D

CASE 8 C.W.-M-F-22 BRONCHIAL ASTHMA	CLINICALLY SENSITIVE	SCRATCH	INTRADERMAL COMPANY			PASSIVE TRANSFER			
						COMPANY I		COMPANY II	
			I	II	III	SENSITIZED AREA	NORMAL SKIN	SENSITIZED AREA	NORMAL SKIN
1 Wheat	+								
2 Egg	?					√	√		
3 Milk	+		±			+		+++√√	+++√√
4 Corn	+					√	√	√	++√
5 Rice	+		±	+					+
6 Rye	?		±	+++					
7 Chicken									
8 Lamb			±						
9 Beef			±					++	+
10 Pea			++√	+			+		++
11 Tomato						+	+	+	
12 Spinach			++	+					++
13 Pineapple				±					++
14 Lemon			+√			√√	√√		
15 Grapefruit				±					+
16 Pear				++				√	√
17 Apple				++				++√	+√
18 String bean				++		+√√	+√√		
19 Potato			±√			√	√	+	+
20 Carrot			++√			√√	+√	√√√	√√√

CASE 9. C.H.-S-M-16. JACKSONIAN EPILEPSY—HAY FEVER.

1 Wheat		±	++	±	±				
2 Egg	+	±				+	+		
3 Milk			+						+
4 Corn		+		+++		√	√	++√	√
5 Rice			++	+				√√√	√√√
6 Rye		±	++	±					
7 Chicken									
8 Lamb			±						
9 Beef						+			
10 Carrot		+		+			+		
11 Pea		±	+			√	√	+√	+√
12 Tomato			+			+√	+√	+√	+√√
13 Spinach			+	+		√	√		
14 String bean				±		√	√	+	++
15 White potato							+		
16 Lemon		+		+		√√	√√	√√	√√
17 Grapefruit				±				√√	√√
18 Pineapple						√	√	√	√
19 Pear				+		+√	√√	+√√	+√√
20 Apple				+		√√	√√	+√√	+√√

NOTE: Blank spaces mean negative reactions.

furnished for experimental purposes by Company II and were prepared according to Coca's technic. All patients except Cases 1, 2 and

TABLE I—CONT'D

CASE 10 H.C.-S-M-24 BRONCHIAL ASTHMA	CLINICALLY SENSITIVE	SCRATCH	INTRADERMAL COMPANY			PASSIVE TRANSFER			
						COMPANY I		COMPANY II	
			I	II	III	SENSITIZED AREA	NORMAL SKIN	SENSITIZED AREA	NORMAL SKIN
1 Wheat	?								
2 Egg	+								
3 Milk	+				√				
4 Corn				√					+
5 Rice			±	++ √√					
6 Rye			±	++					
7 Chicken			++						
8 Lamb									
9 Beef			++						
10 Carrot			√				+		+
11 Pea				+					+
12 Tomato			+						
13 Spinach									
14 String bean			++√	√					
15 White potato			+				+		
16 Lemon			±	+					
17 Grapefruit			±	+					
18 Pineapple			±	√					
19 Pear			±√	±√					
20 Apple			±	++√					

CASE 11. B.W.-M-M-42. GASTROINTESTINAL ALLERGY.

1 Wheat	+					+			
2 Egg	+		±√			+	+		
3 Milk	+					+	+		
4 Corn				√					
5 Rice				+√ √					
6 Rye									
7 Chicken							+		
8 Lamb						+	+		
9 Beef									
10 Carrot									
11 Pea			√						+
12 Tomato			+			+	+		+
13 Spinach				+			+		+
14 String bean				++					+
15 White potato							+		
16 Lemon			+√	+			+		
17 Grapefruit									
18 Pineapple							+		+
19 Pear	+			++					
20 Apple	+			++			+	+	+

3 were tested with extracts of wheat, egg and milk prepared by Coca's method by Company III. This company did not furnish the other requested food extracts.

TABLE I—CONT'D

CASE 12 D.N.-M-M-45 PERENNIAL HAY FEVER	CLINICALLY SENSITIVE	SCRATCH	INTRADERMAL COMPANY			PASSIVE TRANSFER			
						COMPANY I		COMPANY II	
			I	II	III	SENSITIZED AREA	NORMAL SKIN	SENSITIZED AREA	NORMAL SKIN
1 Wheat									
2 Egg	+						+		
3 Milk	+		√						
4 Corn									
5 Rice				±√					
6 Rye									
7 Chicken								+	
8 Lamb			√						
9 Beef									
10 Carrot						+	+		+
11 Pea								++	++
12 Tomato								++	++
13 Spinach									
14 String bean									
15 White potato			±	√					+
16 Lemon						+	+		
17 Grapefruit									
18 Pineapple			√						
19 Pear									
20 Apple			√	±√					

CASE 13. D.B.-F-14. BRONCHIAL ASTHMA.

1 Wheat				+					
2 Egg	+								
3 Milk	+								
4 Corn	+			+		√	√	√	++√√
5 Rice									++√√
6 Rye				+					
7 Chicken									
8 Lamb									
9 Beef						+		+	+
10 Carrot									
11 Pea									
12 Tomato			+						
13 Spinach			+						
14 String bean								+	
15 White potato								+	
16 Lemon			+					√√	√√
17 Grapefruit			+						
18 Pineapple			+						
19 Pear			+						
20 Apple			++					+++	√

TABLE I—CONT'D

CASE 14 A.A.-M-F-29 MIGRAINE	CLINICALLY SENSITIVE	SCRATCH	INTRADERMAL COMPANY			PASSIVE TRANSFER			
						COMPANY I		COMPANY II	
			I	II	III	SENSITIZED AREA	NORMAL SKIN	SENSITIZED AREA	NORMAL SKIN
1 Wheat	?								
2 Egg	+								
3 Milk	+		±√			+	+		
4 Corn	+								
5 Rice	+							+	+
6 Rye	?								
7 Chicken									
8 Lamb									
9 Beef			√						
10 Carrot				+√					
11 Pea				++				+	+
12 Tomato				±					
13 Spinach				+					
14 String bean			√					+	
15 White potato	+								
16 Lemon			±						
17 Grapefruit									
18 Pineapple			±	+					
19 Pear			√	±					
20 Apple	?			++√					

The data in Table I show the various foods to which these seven patients have been found to be clinically sensitive by several eliminations and additions to the respective foods to their diets. Thus, Case 1 was clinically sensitive to wheat, egg, milk and tomato. The data in Columns I and II indicate the skin reactions obtained after careful intradermal injection of from 0.02 to 0.03 c.c. of the indicated food extract of Companies I and II. In Column II it is indicated that Cases 4, 5, 6 and 7 were also tested with the three food extracts obtained for testing purposes from Company III. Most of these patients were clinically sensitive to other foods and a few to condiments not listed in the tables. Moderate or severe allergy to a large number of foods of all types existed in Case 5 and especially in Case 7 which patient was able to eat only the elimination diet indicated below his data in the table. With the addition of dicalcium phosphate and viosterol, however, this patient's metabolic and nutritional requirements were satisfied.

In analyzing the results obtained in the testing of these seven patients, the striking conclusion to be drawn is that many suspicious, positive and delayed reactions occurred to foods to which no clinical sensitizations existed and that the results obtained with the extracts of the three different companies were not at all comparable. It is evident that test-negative diets based on negative skin reactions would

have failed to exclude all the foods productive of the symptoms even though all three commercial extracts had been utilized on each individual who had previously given negative scratch reactions.

The data on Cases 8 to 14 are tabulated separately for each case. They were clinically sensitive to from 1 to 5 foods listed, and were tested intradermally with the 20 foods furnished us by Companies I and II and with the 3 foods furnished by Company III. In addition the sterile blood serum of each of these seven patients was injected into 40 skin areas of a volunteer medical student in order to execute Walzer's[13] indirect skin testing by the Prausnitz-Küstner method. Three days later the extracts of the 20 foods of Companies I and II were injected into these sensitized areas and adjoining unsensitized areas for control purposes. Thus each of the seven students subjected himself to over 120 injections. The students used had been shown to be capable of giving positive pollen reactions in areas sensitized with the serum of a pollen sensitive individual. A careful analysis of the immediate and delayed reactions obtained in these last seven cases indicates that the clinical food sensitizations could not have been determined by intradermal skin testing or by the use of the passive transfer indirect test with these food extracts in these patients who had failed to react to the scratch tests. The number of positive and delayed reactions in the unsensitized skin of these students is noteworthy and increases the difficulty of evaluation of such reactions in patients.

In order to test the relative value of the various extracts used for intradermal testing, patients who gave large reactions with the dry allergens of Company I were tested intradermally with the different extracts of the same foods as shown in Table II. The results obtained in the wheat sensitive patients indicate that the 1:200 dilution made by the extraction of the dry allergen used for scratch testing was superior to products II and III made by Coca's technic and that the 1:1000 dilution from a private laboratory was too weak. The same conclusions appertain to the studies on the milk sensitive patient. The large reactions from milk No. 4 obtained from another allergist and from milk No. 5 prepared in my laboratory by Coca's technic suggest that the commercial products II and III had deteriorated even though recently obtained from both companies. Studies on the egg sensitive patients show that all three commercial extracts gave good reactions.* These results indicate the necessity of determining the activity of all intradermal extracts by tests on patients who give definite scratch reactions to foods which are productive of clinical sensitizations to be sure that

*I have had an opportunity to confirm the activity of most of the dry allergens of Company I on clinically sensitive patients. The other food allergens of Company II have not been tested on clinically sensitive patients, but the results are reported and are important since the extracts are being distributed to the medical profession with the assurance that they are active and stable.

TABLE II

COMPARATIVE SCRATCH AND INTRADERMAL SKIN TESTS WITH VARIOUS FOOD ALLERGENS

SCRATCH	FEMALE AGED 45	MALE AGED 25	SCRATCH	MALE AGED 67	SCRATCH	FEMALE AGED 5	FEMALE AGED 7
Wheat—Whole	++	++++	Milk—Whole	++	Egg—Whole	++	++
Wheat—Globulin	+++	++++	Milk—Lactalbumen	0	Egg—White	+++	+++
Wheat—Glutenin	±	0	Milk—Casein	++	Egg—Yolk	+	++
Wheat—Leucosin	++	+++++	Milk—Cheese	+++	Egg—Ovomucoid	+++	+++
Wheat—Proteose	++	+++++			Egg—Ovovitellin	±	0
INTADERMAL			INTRADERMAL		INTADERMAL		
Wheat—1 (1–200)	+++	++	Milk—1 (1–200)	++	Egg—1 (1–200)	++++	+++
Wheat—2	+	0	Milk—2	0	Egg—2	+++	+++
Wheat—3	+	0	Milk—3	±	Egg—3	+++	+++
Wheat—4 (1–1000)	±		Milk—4 (Casein)	++++			
			Milk—4 (Whey)	++			
			Milk—5	++++			

NOTE: Food extracts 1, 2 and 3 were products of Companies I, II and III. Expiration date on wheat—3 was June 2, 1934. Expiration date of milk —3 was April 4, 1934. Products 4 and 5 were from private laboratories.

the intradermal extracts used are active and capable of giving positive reactions in patients clinically sensitive to such foods. It is also apparent that the 1:1000 dilution of a dry food allergen may fail to react in a sensitive individual especially if the scratch tests are negative. I have found it safe and advisable to use routinely a 1:200 dilution of a 1:50 extract of a dry allergen intradermally in patients *who have reacted negatively to the scratch test.*

COMMENT

1. When definitely positive skin reactions to food allergens are present, they have usually been shown by the initial use of the scratch test. The further use of the intradermal test with those allergens which have given negative or suspicious reactions to foods yielded positive and delayed reactions, many of which occurred to foods not productive of allergic symptoms. Coca[17] recently stated that the scratch test done with active allergens gives as much information as does the intradermal test. Peshkin has held this view moreover since 1927.[18] As a check on the scratch test, however, it is advisable to test the patient intradermally with active extracts of those foods which have failed to give definite scratch reactions. The importance of scratch reactions from the delayed to the 3-plus has been confirmed by many investigators and they should suggest active or potential allergy. But such clinical allergy cannot be ascertained without diet trial with the foods in question.

2. Intradermal tests with foods should be done with extracts of those important foods which have given negative, suspicious or one-plus scratch reactions. Testing with food extracts which have given one-plus scratch tests must be carefully done to prevent constitutional symptoms. The ability of such food extracts to show positive skin reactions should be determined as indicated in Table II before depending upon such commercial or private extracts for diagnostic information. Such evaluation of food extracts must be carefully done to prevent severe allergic reactions.

3. The data in this paper indicate that many positive and delayed reactions may be obtained to foods to which no clinical allergy exists. Coca, Walzer and Thommen[13] emphasize that "a positive reaction indicates only a possible etiologic factor in the causation of atopic symptoms." Certain individuals have irritable skins which undoubtedly yield false reactions especially to the intradermal test. This is also true to a lesser degree of the scratch test. It is recognized that dermal and mucous membrane sensitivity may differ. The large number of reactions obtained by the intradermal test may also be due to nonspecific influences such as trauma from the injection,* extractives or histamin-like bodies which are present in the allergens. Coca, Walzer and Thom-

*Lewis found that 23 per cent to 25 per cent of normal individuals have an exaggerated dermographic response.

men[13] recently stated that food allergens especially contain certain irritating substances. Smyth and Bain[19] agree with Lewis who states that the liberation of a toxic substance that reacts on blood vessels and nerve endings in the skin cells may give rise to false reactions especially with the intradermal test. They also emphasize that skin test phenomena and the capacity to react clinically are independent variables. It is to be appreciated that the actual principle of the most carefully prepared food allergens which are responsible for the skin reaction is still uncertain. In my experience, many positive and especially delayed skin reactions to foods are not indicative of clinical or even potential allergy. If potential allergy is indicated, exclusion of such foods is not necessarily advisable.

4. Diets therefore based entirely on negative skin tests may exclude foods which are not allergy producing, and are liable to include foods which are responsible for allergic symptoms. Thus Case 5 gave a four-plus reaction to carrots. Case 6 gave a two-plus intradermal reaction to apple and a three-plus by passive transfer to apple. Both of these foods can be eaten without any symptoms whatsoever, whereas the same patients did not react to several food allergens which were productive of symptoms. That many other one- and two-plus reactions by both methods of testing were obtained illustrates the same point.

5. The lack of positive skin reactions has been ascribed to a fixation of reacting bodies in the shock tissues in which the allergic symptoms of the patient arise or to the lack of skin sensitizing bodies in the circulating blood and the skin itself. Both possibilities are entirely likely. There is no reason why gastrointestinal allergy or bronchial asthma necessarily has to be associated with the presence of skin test or sensitizing bodies which give reactions to all or any of the causative foods. Vaughan[10] states, "This may be because only certain tissues of the body are sensitive (intestinal tract) while others (skin) are not." His discussion of the possible explanations of the negative skin reaction to foods is valuable. The fact that the negative skin reaction may be due to a refractory phase associated with temporary desensitization is recognized but the retesting of many patients has yielded helpful information infrequently. Coca, Walzer and Thommen[13] state, "Skin reactions are negative in most clinical forms of hypersensitiveness which are not based upon a reagin mechanism. This includes many cases of food idiosyncrasy causing angioneurotic edema, gastrointestinal disturbances, urticaria, vasomotor rhinitis, Henoch's purpura, migraine, etc." When positive reactions exist, it is fortunate, and they occur frequently enough to justify the routine use of scratch and supplemental intradermal skin testing to obtain the diagnostic help that they offer.

It may be that there is less variation in the reacting ability of the skin than theoretical considerations and animal experiments might

indicate. Skin testing therefore takes a subsidiary place to diet trial in the diagnosis of food allergy, which like other problems of medicine places a premium on clinical experience and judgment as well as on laboratory technic, carefully executed with properly prepared and standardized reagents and solutions. The fact that the method of preparation and extraction of the food allergens may destroy the reacting substance and that the dilutions themselves lose their activity more or less rapidly must also be remembered.

CONCLUSIONS

1. The failure of certain patients to react by the scratch and intradermal methods to all of the foods to which clinical allergy exists is demonstrated.

2. The occurrence of many suspicious, positive and delayed reactions especially with intradermal testing with extracts of foods which are not productive of allergy is illustrated.

3. The scratch test with active allergens well executed will demonstrate in most patients those foods to which skin sensitizing bodies exist. The intradermal test should then be done with active extracts of those important foods to which negative scratch reactions have occurred. False positive reactions without clinical symptoms and nonspecific reactions must be remembered.

4. The activity of a food extract for intradermal testing should be determined by definite intradermal reactions obtained in a patient who is clinically sensitive to such a food and who gives a good scratch reaction to that food. Certification of such activity should form the basis of acceptance of food allergens and extracts by the Council of Pharmacy.

5. The importance of diet trial as a determinant of the clinical allergy to all reacting foods is necessary.

6. I have found that a 1:200 dilution of a 2 per cent extract of an active dry food allergen in glycerin-salt solution in patients who have given negative reactions by the scratch test is satisfactory for intradermal testing.

7. When diets based on skin reactions alone do not control symptoms suspected of food allergy, the necessity of trial diets such as the "elimination diets" modified by positive skin reactions or histories of idiosyncrasies to foods is advisable for diagnostic purposes.

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THE IMPORTANCE OF ADEQUATE TESTS AND THEIR PROPER EVALUATIONS*

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IN THE constitutional condition known as allergy the skin shows a specific sensitivity that makes possible a diagnosis through protein skin tests. That there are serious difficulties in the interpretations of skin tests must not only be admitted but thoroughly understood. But with all its difficulties, skin testing remains the most fundamental means of diagnosis at our disposal, and every effort for the full utilization of this valuable diagnostic method should be made. The factors upon which success depends are the reliability of the materials used, the extent and method of testing, the selection of the skin's surface, and, most important of all, the evaluation of the reactions in the single individual in connection with the clinical history. The evaluation must be made by an experienced worker.

The purpose of this paper is to add to the discussion certain conclusions arising from the author's experience with testing under controlled conditions in a sanatorium where all the ordinary inhalants found in homes or places of business are eliminated, and special diets are prepared for each person. In fact, all possible contracts are controlled. These conclusions will at the same time argue against the advocacy of some specialists in this field, of the use of only a small group of allergens found most often to be the cause, and also against elimination of foods, such as in the so-called elimination diets, and against the elimination of groups of inhalants not based on specific tests.

There are good reasons for vigorously opposing any such simplification of the skin tests for diagnosis as the use of a small number of allergens. In the first place, the patient may and doubtless will obtain an incorrect estimate of his security. If he chances to be sensitive to a protein not included within a brief list of fifty or sixty, and if his contacts are not infrequent, the patient's faith will ultimately turn to skepticism concerning any possible relief. This is, of course, a harmful result. Second, success depends upon the cooperation of the patient. He should strive for entire relief, but such a desirable end cannot be secured without the adequate knowledge which comes from complete testing. Third, there are cases in which the brief tests are negative, and yet the patient would be proved allergic by thorough testing. Thus, the diagnosis is inadequate although accepted as ade-

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quate by the patient. The essence of the matter is this. In allergy, as in other fields, an inadequate diagnosis is often worse for the patient than none at all. Every allergic person should have the benefit of a thoroughly adequate examination, and every practitioner should realize the possible harm to the patient from an examination not exhaustive enough to obtain results.

Interpretation of reactions must naturally be based on method as well as experience. The purity of testing material must be absolutely trustworthy. For this reason, many allergists have established their own laboratories. Or one may purchase from several reliable laboratories and by constant comparison make certain of the purity and uniformity of the product. I find the latter method satisfactory.

It is well known that skin sensitivity varies from one part of the body to another. The area on the back above the waist line gives an ample surface, and the noticeable variability in the person is removed when the tests are confined to this area. This area gives sufficient surface for a comparison of the tests.

The greatest difficulty of testing arises in the variation and significance of the reaction with different persons. These individual differences show all gradations, but for the purpose of discussion cases may be separated into four representative types. These will be described as normal reactions, excessive reactions, slight reactions, and negative reactions. I propose to mention the significant features of the evaluation of testing by referring to these types separately. This description will be more clearly comprehended if as a preliminary I state the nature of the cases received and the use of the sanatorium. I am located in a small university city of 15,000. Consequently, most of my patients are from distant points. It is perhaps safe to assume that compared with usual clinical cases, my cases are, on the average, more severe. At the same time this condition of nonresident cases early resulted in the use of the sanatorium. Experience showed such a marked improvement in satisfactory results by the use of the sanatorium that now residence there is obligatory for all nasal and bronchial cases.

Returning now to the methods, two general statements can be made. Complete scratch tests are routine for all cases and indicate at once the type to which a case belongs.

The scratch tests are followed by intradermal tests. Second, there is no standard reaction, nor is the size of a reaction an indication of its importance. The importance of any reaction can be evaluated only in connection with the clinical history of the patient. In the first group, the normal type, there are well-defined reactions to the scratch tests, and they are consistent with the clinical history. The intradermal tests add but little to the diagnosis. In this group I find with many cases that inhalants are more important than foods. With a

smaller number, the reverse is true. Consequently, with the former, living in the sanatorium produces an immediate improvement. With some of these no elimination of foods is found necessary. Perhaps nothing more need be said concerning the normal type.

In the second group, that of excessive reactions to scratch tests, the reactions are not only large but too numerous. Many of these patients remark that they have been tested before and have been told they reacted to everything. In this group the intradermal tests are unnecessary. This group requires a very careful study of possible contacts, with a view in each case of determining the significance of the reactions. If there is a correspondence of reaction and contact, this reaction is considered important. Then with the opportunities offered in the sanatorium, suspected foods are given a clinical test for significance. With these two methods it is possible to reach a satisfactory diagnosis of a case. Of course, diagnosis is difficult but one can expect to have distinct success in all but a very small percentage of such cases. One typical case may be mentioned. This patient had been described by a well-known clinic as an allergic phenomenon on account of her excessive reactions. It required three weeks' residence in the sanatorium to test the relative importance of her food reactions and to be able to give adequate directions for her subsequent care.

In the third group are those for whom the scratch tests give only slight reactions. With these one must depend on intradermal tests, and often a reaction which would be indicated by slight erythema is of the utmost importance. In these cases, in order to obtain and to be certain of these slight reactions, it is necessary to retest and to establish the persistence of the erythema for any protein. The control of the environment in the sanatorium is also most valuable, because the more questionable the interpretation of the tests, the more necessary is clinical evidence. In both of these types, excessive and slight reactions, the final diagnosis is, in practice, as reliable as in the normal type.

There are but few cases of the negative reaction type. The patients are usually in poor general condition, they are emaciated, their skin is unhealthy, and many of them have been using adrenalin from months to years. In this group the scratch tests are of no value, and even by intradermal tests one can obtain only slight erythema to an insufficient number to account for the clinical history. The tests do not tell the whole story. One must then rely upon the experiments with foods in the sanatorium. The so-called elimination diets are not satisfactory, because they do not eliminate enough. In such cases we now eliminate all but one or two foods, usually putting the patients, if possible, on a milk diet, including butter and cottage cheese, and building up a diet with as much help as can be obtained from the skin tests.

By referring specifically to four types of cases, there has been made evident the following practice. First, the skin tests are made funda-

mental, and second, every opportunity of securing clinical evidence is utilized. By such thorough and persistent effort, the percentage of diagnoses that agrees with subsequent clinical history can be made very high. It is commonly reported that the literature shows the average diagnostic success to be in the neighborhood of 50 or 60 per cent. Naturally, this includes many records based on inadequate testing.

Every one of our cases is followed for from one to two years. At the outset rather elaborate weekly reports are received and studied. Later, the reports are monthly. Thus, knowledge is obtained of the success of diagnoses. I have no hesitancy in saying that by persistently following the above methods, our records show satisfactory diagnoses in well over 95 per cent of the cases. In short, the methods are as successful as in almost any other branch of medicine.

It is to be borne clearly in mind that I am working with only a few cases, from 8 to 10, at one time, and under ideally controlled conditions.

In the foregoing it is readily admitted that the impossibility of standardized tests introduces difficulties, but it is claimed that, by proper use, tests fail in certainly less than 1 per cent of our cases which exceed several hundred. Further, the tests are reliable and not misleading when properly interpreted. For elimination of foods there is an appropriate use, but it is clearly secondary, except in a very small percentage of the cases.

The points mentioned in this paper are not separately new, but it is believed that the combination of effort described and its success is a contribution to current discussion of diagnosis in allergy.

ALLERGIC RELATIONS OF NORMAL AND ABNORMAL FLORAS OF THE INTESTINE*

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IN PREVIOUS reports[1, 2] I have described in detail some of the chief factors in the specific action of bacteria in relation to asthma and other allergic states, and have presented the results of treatment with bacterial antigens. Reference was made to the pioneer researches of Avery, Zinsser, and a host of others in the field of specific bacterial split products, and an attempt was made to correlate this important knowledge with the needs of allergic practice.

An additional series of results strengthened my belief in the efficacy of a proper administration of bacterial suspensions in carefully selected cases.

The purpose of the present report was to obtain additional details concerning the nature of the bacterial antigens, and to add to the knowledge of their effect. Further study was devoted to the pathogenic organisms of the intestinal tract, bronchi, and other foci, but this investigation was also extended recently to include the action of the so-called normal flora of the colon. These two phases of the subject can be best presented separately, and afterward analyzed in a comparative way. Their effects will be found to differ materially.

FURTHER STUDY OF PATHOGENIC BACTERIA

The preferable method of culturing the feces for pathogens, so as to exclude organisms normally present in the large intestine, has already been described, and need receive only brief mention here. One small platinum loopful of feces, preferably from the last portion passed, is shaken up with 5.0 c.c. sterile 1 per cent sodium carbonate solution, and incubated overnight. Next morning it is again shaken, and then plated out in dextrose blood infusion agar plates, with successive dilutions on the decimal system, so that the first plate contains 0.5 c.c. of the carbonate solution, or 0.1 of the original loopful of stool. The second plate contains 0.01 and the third plate 0.001 of the original loopful. Due to the inhibiting action of the carbonate solution, the normal intestinal flora fails to grow; and in cases of infection with pyogenic organisms, the plates contain evenly distributed colonies entirely similar to those seen in the plating out of a pure culture.

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The differential counting of pathogenic bacteria then becomes a simple matter of mathematics. The number of these, including *Streptococcus viridans*, *hemolyticus*, and *nonhemolyticus*, *Pneumococcus*, *Staphylococcus aureus*, and others, often totals many millions per loopful of stool.

In testing for bacterial sensitization the intradermal test has been employed as a routine. Two-hundredths of a cubic centimeter of the bacterial preparation, either washed organisms or sterile unheated filtrate, is injected by this method, and reactions are read in fifteen to thirty minutes, and again in eighteen to thirty-six hours. In occa-

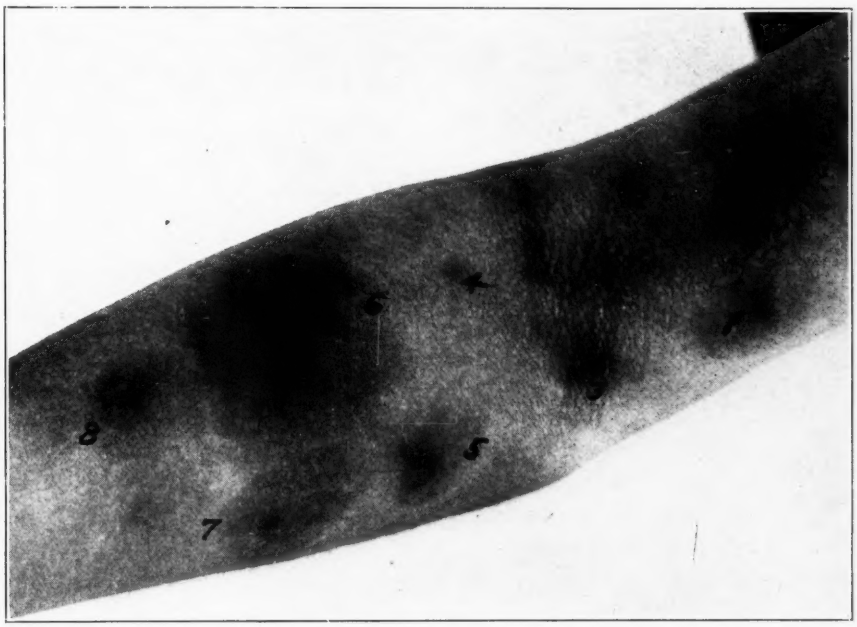

Fig. 1.—Twenty-four-hour intradermal reactions of streptococcus preparations of patient G. G. referred to in Table II. (See text.)

1. Washed *Streptococcus viridans* from sputum;
2. Sterile unheated *Streptococcus viridans* filtrate from sputum;
3. Washed *Streptococcus hemolyticus* from sputum;
4. Sterile unheated *Streptococcus hemolyticus* filtrate from sputum;
5. Washed *Streptococcus viridans* from stool;
6. Sterile unheated *Streptococcus viridans* filtrate from stool;
7. Washed *Streptococcus hemolyticus* from stool;
8. Sterile unheated *Streptococcus hemolyticus* filtrate from stool.

sional instances the bacterial preparation contains sufficient reactive substance to produce prompt wheal formation, the significance of which is substantiated by subsequent clinical results.

More often, however, the early reaction is negligible, representing merely the cutaneous response to traumatism, the true allergic reaction being represented by the Dick type of erythema occurring in fifteen to thirty-six hours. This reaction has been accepted throughout the present study as a measure of sensitivity.

Of 610 stool cultures for pathogens, obtained in allergic cases in the past three years and nine months, nearly all were tested on the patient's skin, but in addition to this many were tried on other subjects, both normal and allergic. Varying degrees of reaction were observed. A few failed to react, either on the patient's skin or on others. A more common observation was a strong reaction on the patient's own skin (Fig. 1), and little or none on others. The protocols in Tables I, II, and III are fairly typical.

TABLE I

TWENTY-FOUR-HOUR INTRADERMAL REACTIONS OF PATIENT M. S. R. TO SEVERAL STRAINS OF STREPTOCOCCUS VIRIDANS

STRAIN	ORIGIN	HEATED TO	REACTION
M. S. R.	Stool	60° C. 1 hour	+++ 20×40 mm.
M. S. R.	Stool	100° C. ½ hour	+ 10×10 mm.
M. S. R.	Sputum	60° C. 1 hour	±
F. A. P.	Stool	60° C. 1 hour	±
M. C. R.	Stool	60° C. 1 hour	–

TABLE II

TWENTY-FOUR-HOUR INTRADERMAL REACTIONS OF SEVERAL PATIENTS TO STREPTOCOCCUS VIRIDANS STRAIN, G. G.

PATIENT TESTED	REACTION TO OWN STRAIN	REACTION TO STRAIN, G. G.
G. G.	+++ 25×25 mm.	+++ 25×25 mm.
A. A.	++ 20×20 mm.	—
F. A. P.	++++ 55×40 mm.	—
R. B. T.	±	±

The cases in Tables I and II were selected at random to show the variety of reactions encountered. Most of them reacted well to their own organisms, but little or not at all to others. One patient, R. B. T., failed to react to either her own or to another.

One *Streptococcus viridans* culture, that from the stool of patient F. A. P., received detailed study because of its wide reactivity. This patient, himself, gave a ++++ twenty-four-hour intradermal reaction. Of 29 other allergic individuals tested with his bacterial suspension, 23 reacted strongly. Only one subject, M. S. R., gave a greater reaction to his own strain than to that of F. A. P. All the others uniformly responded to F. A. P. as strongly, and usually more so, than to their own autogenous suspensions. (Table III.)

It is apparent that this *Streptococcus viridans* strain, F. A. P., diverges from the usual rule. Most of those which have been encountered in the series have displayed varying degrees of type specificity, but strain F. A. P. manifested a highly inclusive species specificity which has overshadowed, in most instances, the weaker type specificity of other culturally similar organism. Clawson and Wetherby[3]

reported a similarly protective strain of *Streptococcus viridans* recovered from a case of acute rheumatic fever.

All of my observations in this series lead me to agree with Clawson, and others, that the sensitization phenomena with *Streptococcus viridans* are allergic, and not of the nature of nonspecific protein reactions. Varying degrees of type specificity appear in different strains, but may be surpassed in many instances by a more potent species specificity.

TABLE III

TWENTY-FOUR-HOUR INTRADERMAL REACTIONS TO STREPTOCOCCUS VIRIDANS, F. A. P.

PATIENT TESTED	REACTION TO OWN STREPTOCOCCUS VIRIDANS		REACTION TO STREPTOCOCCUS VIRIDANS OF F. A. P.	
M. A.	+++	27×27 mm.	++++	55×35 mm.
A. A.	++	20×20 mm.	++++	70×30 mm.
M. B.	—		+++	35×25 mm.
E. G. B.	++++	50×30 mm.	++++	65×30 mm.
E. B.	—		—	
H. C.	++	25×15 mm.	++++	45×35 mm.
Mrs. A. D.	++	25×17 mm.	+++	40×30 mm.
P. E. D.	—		++++	55×25 mm.
Miss B. G.	++	20×20 mm.	++++	55×35 mm.
R. G.	+	10×10 mm.	+++	30×25 mm.
B. G.	—		—	
A. H.	++++	40×30 mm.	++++	45×32 mm.
F. V. H.	++	25×20 mm.	++++	40×35 mm.
L. B. K.	—		++++	50×30 mm.
M. K.	++++	40×40 mm.	++++	45×35 mm.
E. K.	—		+++	35×25 mm.
F. D. K.	—		++++	55×40 mm.
H. L.	++	18×18 mm.	++++	70×70 mm.
R. L.	+	10×10 mm.	+	10×10 mm.
J. M.	—		+++	40×20 mm.
M. S. R.	+++	40×20 mm.	±	
K. R.	—		+++	35×25 mm.
M. R.	—		+++	45×20 mm.
E. M. S.	—		+++	40×25 mm.
H. W. S.	++	20×20 mm.	++++	65×40 mm.
R. B. T.	±		±	
G. C. W.	++	25×20 mm.	++++	50×35 mm.
A. W.	+++	30×25 mm.	++++	55×55 mm.
N. F.	±		±	

Cutaneous Protection Tests

Various workers have observed that subsequent intradermal inoculation in the exact site of a previous similar inoculation with the same allergen usually reveals local desensitization. It is generally agreed that this local protective process occurs promptly, while general desensitization usually requires a number of successive injections of the allergen.*

*An interesting example of a fortuitous local protection result occurred under my observation recently. Culture of the skin about the anus in a bedridden patient with pruritis ani yielded *Streptococcus viridans* and *Staphylococcus aureus*, both in large numbers. Intradermal tests on the arm gave strong twenty-four-hour erythematous reaction in both instances. Daily small injections of the combined bacterial suspension in scattered points about the anus cleared up the distressing condition so completely in the course of a very few days that no reasonable doubt remained as to the agent responsible for the improvement. This appears to be one of the few occasions of a local desensitization which is not only diagnostic, but therapeutic as well.

Such local protection tests were done with a large percentage of my bacterial antigens. Usually a single intradermal inoculation produced almost or quite complete inhibition of the local reactivity within two or three days. Only occasionally were several successive injections in the same site necessary to produce this result.

Crossed protection tests were done by inoculating intradermally, first with the patient's own bacterin, and several days later with another strain in the same site. The reverse process was also carried out. The results varied. Some strains cross protected partially, others completely. Only one, the strain F. A. P., already referred to, displayed an almost universal ability to protect in any skin more effectively than the patients' own strains. On the other hand, most patients' strains failed to protect well against the more reactive F. A. P. strain. These observations furnish another evidence that type specificity in *Streptococcus viridans*, although present in varying degrees, may be overshadowed by the much stronger species specificity of certain strains.

Having found a specimen of *Streptococcus viridans* with such broad protective power, the possibility at once suggested itself of using its bacterin in the desensitization of other individuals having a culturally similar organism. This proved successful in several of my cases, of which the following will serve as an example.

Case Report.—Patient M. A., a woman of middle age, had suffered with asthma over a period of eighteen years. Repeated autogenous vaccine courses, always with streptococcus strains, had usually given relief. A few months ago her asthma recurred. Stool culture again gave *Streptococcus viridans* in large numbers. Intradermal tests showed her more reactive to strain F. A. P. than to her own. (Table III.) She was accordingly started on a series of inoculations with this strain with the result that she became promptly and completely desensitized.

Other similar results could be cited. I still follow the practice of treating most of my bacterial cases of asthma and other types of allergy with autogenous vaccines of the organisms recovered, and the results have usually been satisfactory. It seems entirely plausible, however, in certain cases to substitute for the autogenous bacterin a culturally similar, but more strongly antigenic, strain such as the F. A. P. organism referred to.

Other Properties of Bacterial Antigens

Space does not permit a detailed consideration here of the various pathogens predominating in stool culture. These were referred to previously and include *Streptococcus viridans, hemolyticus* and *non-hemolyticus, Pneumococcus, Staphylococcus aureus*, and occasionally others. All of these proved important.

In the case of the various streptococci, repeated tests were made with suspensions of washed organisms, killed at 60° and 100° C. respectively. I have been surprised to find that, in the majority of instances, the antigen withstood poorly the higher temperature. This suggests the possible presence of other antigenic factors besides the known heat-stable O-antigen.

Sterile filtrates failed to disclose any information of importance, but require further study.

Each of my attempts to obtain a potent coagulable protein from thoroughly ground streptococci failed.

The possibility of the existence of toxins or other specific factors besides the carbohydrate-nucleoprotein combination of Avery, Zinsser and others, still requires investigation.

Discussion

At the present writing we are still concerned, in the case of the pathogenic organisms, with a bacterial O-antigen which certainly withstands well a lethal heating to 60° C. for one hour. Its effects are not of the nature of nonspecific protein reactions, but a combination of type specific and species specific sensitization phenomena, both of which are utilizable in treatment. Desensitization to bacterial allergens is usually adequately accomplished by subcutaneous injections of small doses of heat-killed organisms, with or without the inclusion of sterile unheated filtrate. In certain cases intravenous inoculation produced more prompt desensitization than the subcutaneous method.

THE SO-CALLED "NORMAL INTESTINAL FLORA"

My interest has been attracted to the antigenic properties of this group of organisms by the reports of Dorst and his associates.[4, 5, 6] Utilizing the intradermal reaction as early as 1927, these workers studied the intestinal bacteria in cases of arthritis, sinusitis, bacterial asthma, colitis, cholecystitis, and certain skin infections. They expressed the belief that in many instances the reactions obtained represented an allergic sensitization of the mucous membranes of the body to organisms which are frequently considered nonpathogenic. They obtained few reactions to the intestinal group of organisms in control subjects, but found 26 out of 30 selected gastrointestinal and other patients reactive.

These authors attempted desensitization to the "normal flora" in a considerable series of cases falling in a category that has been termed the "irritable colon." This included conditions which had received a questionable diagnosis of autointoxication, spastic or mucous colitis, chronic appendicitis, peptic ulcer, or chronic cholecystitis. The usual result of the vaccine treatment was a gradual disappearance of skin sensitivity with improvement or cessation of clinical symptoms.

They reported that these killed suspensions of their intestinal organisms, when subjected for twelve hours in vitro to the action of 1 per cent sodium ricinoleate, lost their skin reactivity and consequently their toxicity, but that they retained their antigenic properties unimpaired.

Fig. 2.—Five-hour intradermal reactions of *B. coli* preparations of patient, Mrs. E. B. (Old scratch marks also in evidence)
1. Suspension of washed *B. coli* from stool;
2. Sterile unheated filtrate of same *B. coli*;
3. Suspension (washed) of second *B. coli* from stool.

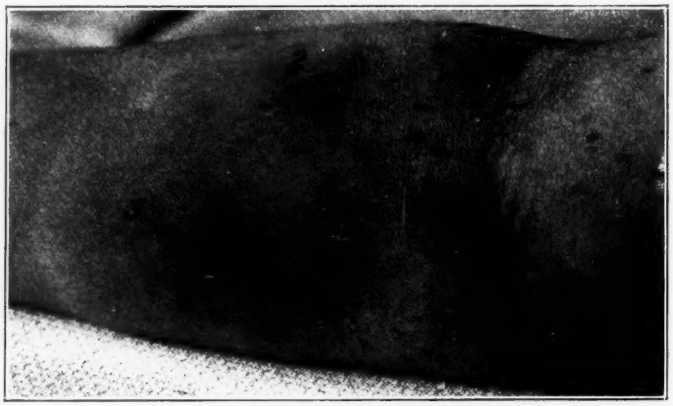

Fig. 3.—Twenty-four-hour intradermal reactions of patient, Mrs. E. B., corresponding with five-hour reactions shown in Fig. 2. (Note the large size of Reaction 3. Same numbering as in Fig. 2.)

Author's Series

I have recently cultured the so-called normal flora of 200 fecal specimens in an attempt to evaluate the importance of this group of bacteria in asthma and other allergic conditions. The results are still incomplete, but I hope at least to contribute some information regarding the properties of the antigens involved.

Most of the cultures were isolated by the Bacteriology Department of the University of Oregon Medical School, and turned over to me for experimental study. As would be expected, most of them were lactose fermenters. The *B. coli* group was represented by the usual varieties, *commune, communior, neopolitanum, acidi lactici. B. aerogenes, morgani, dispar,* and *typhosum,* and the salmonella group appeared in a few cultures. A complete tabulation of these has no place in an article of this scope.

Of the cultures carefully isolated at the Medical School, 77 have thus far been tested intradermally on patients. In each instance one portion of the suspension of washed organisms was killed at 60° C. for one hour, the other at 100° C. for one-half hour, and both were usually applied in separate tests.

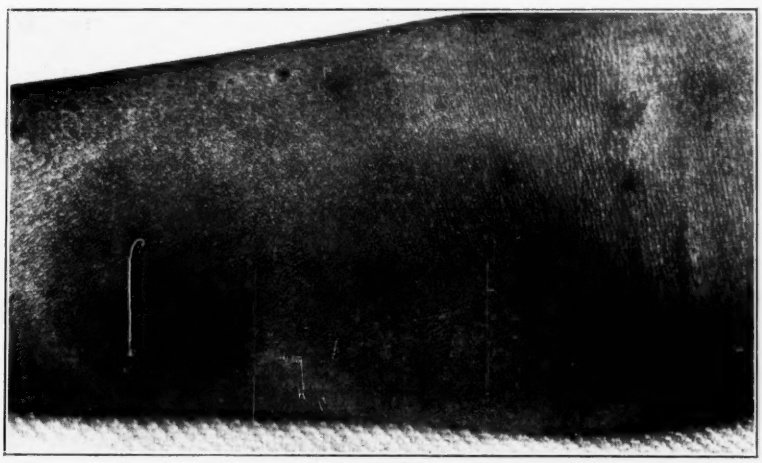

Fig. 4.—Twenty-four-hour intradermal reactions of *B. coli* preparations of patient, Mrs. E. G. The two large erythematous reactions with central roseola are similar inoculations with washed organisms. The other insignificant reaction is from sterile unheated filtrate of the same organism.

The immediate reaction to the intradermal test is not significant. The delayed reaction commences in three to ten hours, has a slightly raised reddish area of variable extent (Fig. 2) which usually increases continuously in size during the first twenty-four or even thirty-six hours (Figs. 2, 3, 4), and is often accompanied by local heat, tenderness, and tenseness of the surrounding tissue. Malaise, chilling, aching of joints and muscles, loss of appetite, and one or two degrees rise of temperature are frequent symptoms, sometimes with a recrudescence of asthma or other allergic manifestations.

Of the 77 cultures tested intradermally, only four failed to produce an erythema at least 25 mm. in diameter, and most of the reactions were much larger. Many involved nearly the whole width of the forearm, often accompanied by a central roseola. Similar reactions occurred with the *B. coli* group, the Salmonella group, *B. dispar, aero-*

genes, typhosum, morgani, and all the usual intestinal organisms tested. Reaction to the so-called normal flora appeared to be rather the rule than the exception. If this indicates sensitization to bacterial antigen, it follows logically that the frequent instance of these infestations of the colon must have produced an almost universal sensitization to this group of organisms.

A small group of supposedly normal controls was similarly cultured and tested. Each of these reacted intradermally to his own intestinal organism, and likewise reacted to those from the other controls. This observation pointed the need for crossed testing of various strains from patients.

Crossed Testing of Strains

Many cultures have been tested, not only on the patients themselves, but on other patients and on supposedly normal controls. Table IV will serve as an example.

TABLE IV

TWENTY-FOUR-HOUR INTRADERMAL REACTION TO B. COLI OF PATIENT S. M.

PERSON TESTED	DIAGNOSIS	REACTION
S. M.	Asthma	++++ 90×50 mm.
A. A.	Asthma	++++ 70×45 mm.
Mrs. K.	Asthma	++++ 60×38 mm.
R. B. T.	Asthma	++++ 45×40 mm.
R. L. B.	Nonallergic control	++++ 60×40 mm.
R. W.	Dermographia	++++ 90×55 mm.

Many similar crossed testings were made, and always with the same result. The *B. coli* which reacted with the patient always reacted with others, and this rule applies to all members of the so-called normal intestinal flora which we tried. Equally significant is the fact that the few bacterial suspensions of the normal flora group which failed to give a reaction with the patient also failed with other individuals tested. The difference in reactivity seems to reside in the bacteria themselves rather than in variations in the human.

Local Cutaneous Protection Tests

The technic employed in these tests consisted of an intradermal inoculation of 0.02 c.c. of bacterial suspension into the arm, followed two or three days later by another injection of the same suspension, or in some cases other suspensions for comparison, in the original

TABLE V

SUCCESSIVE INTRADERMAL INOCULATIONS OF B. COLI IN SAME SITE. PATIENT R. F.

DATE	DOSAGE	REACTION
4/ 6/33	0.02 c.c.	++++ 55×40 mm.
4/11/33	0.05 c.c.	+++ 40×35 mm.
4/14/33	0.05 c.c.	++ 27×25 mm.
4/19/33	0.07 c.c.	±

site. A large number of these were done. In most instances a single inoculation sufficed to desensitize locally against subsequent inoculations of the same organism. Only occasionally were several inoculations required, as in Table V.

It may be inferred on fairly safe grounds that sufficient number of properly graduated doses will eventually result in some degree of general desensitization, possibly with clinical improvement of the patient.

Rough (R) and Smooth (S) Strains

Through the cooperation of the Bacteriology Department of the University of Oregon Medical School various cultures were separated into R and S strains. Numerous tests with these failed to disclose any significant difference in reactivity between the two. R and S antigens obtained from a single source produced the same intradermal response in the patient and in controls.

In repeated instances a suspension of an R variant of *B. coli* was injected intradermally into the former inoculation site of the corresponding S variant, and on the other arm the S variant into the original R site. Without entering into tedious detail I am able to state that each protected equally and, as a rule, completely, against the other.

Crossed Local Cutaneous Protection Tests

Just as the R and S variants of a single strain of *B. coli* have reacted similarly on the skin, so also have different strains of *B. coli* from the same individual, or even from different ones. This reactive indifference to strain does not apply in any noteworthy degree, however, to biologic gaps as great as that between *B. coli*, on the one hand, and widely divergent types like *B. dispar* or *aerogenes* on the other.

This same rule applies to local protection afforded by an intradermal reaction against subsequent inoculations in the same site with other organisms. Two strains of *B. coli* which react will almost invariably protect locally, one against the other. On the other hand, *B. coli* fails to protect a local cutaneous site against subsequent injections of widely different types such as Salmonella, *B. aerogenes*, or *B. dispar*. The following will serve as examples:

Patient, Mrs. J. E.		
B. coli	++++	75×70 mm.
Salmonella	+++	40×25 mm.
B. coli in former Salmonella site	+++	40×30 mm.
Patient G. K. H.		
B. coli	++++	50×35 mm.
B. aerogenes	+++	35×30 mm.
B. aerogenes in own original site	±	
B. aerogenes in original *B. coli* site	++	30×20 mm.

Patient, Mrs. M. C. (own strains)		
1. *B. coli* strain 151R	++++	60×45 mm.
2. *B. coli* strain 151S	++++	65×55 mm.
3. *B. coli* strain 151aS	+++	30×30 mm.
4. *B. aerogenes* 151b	++++	70×55 mm.
5. No. 1 reinoculated in site 1	—	
6. No. 4 reinoculated in site 2	+++	35×30 mm.
7. No. 3 reinoculated in site 4	++	20×20 mm.
8. No. 4 reinoculated in site 3	+	20×15 mm.

In the first instance Salmonella has only partially protected against *B. coli*. In the second, *B. coli* has given only slight protection toward *B. aerogenes*, although the latter has protected well toward itself. In the third, *B. coli* has desensitized locally toward itself but failed to desensitize against *B. aerogenes*, while the latter has failed against *B. coli*.

From these and many other comparative tests it appears that the reactions within the *B. coli* group are sharply group specific, but not type specific. Other members of the genus Bacterium seem to have their own group specificities which differentiate them allergically from *B. coli*.

H- and O-Antigens

In case the reader is unfamiliar with the definitions and properties of these two types of antigens he is referred to any of the recent textbooks on bacteriology. The H-antigen, which is thermolabile, is understood to reside in the flagella, while the thermostable O-antigen occurs chiefly in the bodies of the bacteria.

In an attempt to obtain a better understanding of the antigens in these intestinal organisms I have followed two distinct lines of study. The first was to divide the bacterial suspensions into two portions, one of which was heated to a temperature of 60° C. for one hour, the other being killed at 100° C. for thirty minutes to destroy the H-antigen. By the latter procedure a pure O-antigen was presumed to result. In a considerable series of cases the boiled and unboiled fractions were tested intradermally in parallel, but the reactions were in general similar. It appeared that the predominating antigen in these nonmotile and sluggishly motile organisms was mostly of the heat stable O type.

The other procedure consisted of shaking a forty-eight-hour broth culture of the organism with glass beads in the hope of dislodging flagella. It was then filtered through a Chamberland candle in an attempt to obtain the H-antigen in the filtrate in a finely divided form. Six such filtrates were tested intradermally in parallel in two portions, one heated to boiling to destroy H-antigen, the other unheated. In two of these attempts a pure H-antigen was demonstrated in *B. coli* preparations by the fact that the unheated filtrate reacted well, while the boiled portion failed to give any reaction.

In one of these instances the pure H-antigen was cross-tested intradermally with the corresponding O-antigen with the following result.

ANTIGEN	REACTION
1. O-antigen	++++ 70×40 mm.
2. H-antigen	+++ 35×28 mm.
3. No. 1 in original No. 2 site	++ 30×20 mm.

It does not appear that H-antigen has protected completely against O-antigen. Considerably more work along this line will be required before definite conclusions can be reached.

Sodium Ricinoleate (Soricin) Effects

In an effort to explain the detoxication of intestinal bacteria in vitro by soricin as reported by Dorst, I repeated his procedure on three patients. Heat killed autogenous suspensions of *B. coli* were subjected to 1 per cent soricin for twelve hours. The organisms were then washed free of soricin. These I shall designate the soricinized suspensions. These injected intradermally produced no reaction of any importance. Untreated suspensions, on the other hand, gave good reactions. Thus far my results agree with this author.

I question, however, his assumption that the antigenic properties of the vaccines treated for twelve hours with soricin were unimpaired. I found in each instance that a subsequent intradermal inoculation of untreated suspension in the original site of the nonreacting soricinized vaccine resulted in a strong twenty-four-hour reaction (Table VI).

TABLE VI

SODIUM RICINOLEATE (SORICIN) EFFECTS

PATIENT TESTED	TWENTY-FOUR-HOUR INTRADERMAL REACTION TO 0.02 C.C. OF		
	B. COLI SUSPENSION UNTREATED	SORICINIZED B. COLI	B. COLI SUSPENSION UNTREATED IN SITE OF SORICINIZED SUSPENSION
W. McD.	++++ 70×60 mm.	—	+++ 38×20 mm.
F. A. P.	++++ 45×40 mm.	± faint	++++ 50×33 mm.
J. P. S.	++++ 65×55 mm.	± 10 mm.	++++ 60×45 mm.

These results lead me to believe that soricin decidedly impairs the antigenic properties of these bacterial suspensions. I strongly suspect that it destroyed the antigen, and suggest further experimentation along this line.

The observations above have no essential bearing on the reported benefit following the enteric use of soricin. I employ it in selected cases, but am not yet in a position to evaluate its results.

Autogenous Vaccine Treatment

I am employing this form of therapy as recommended by Dorst in an increasing number of cases with small doses of autogenous sus-

pensions of washed organisms. It is too early to give figures on results, but I am convinced that benefit has already followed in certain instances.

It was found that members of the genus Bacterium were group specific. Thus the *B. coli* group acted indifferently among themselves, the aerogenes group among themselves, and so on. It follows logically that vaccine therapy with these organisms, if practiced, may resolve itself into the selection and employment of a limited number of stock strains, each of which should serve adequately for its own group.

Summary

Nearly all patients and normal controls reacted to intradermal inoculations of their own suspensions of "normal flora" organisms. Moreover, the suspension which reacted with one individual always reacted with every individual tested. Possibly this constitutes a sensitization phenomenon, but if so, the common occurrence of most of these organisms in the intestinal tracts must have sensitized universally. The alternative of this is that the bacteria themselves may contain some group specific aggressive factor which has not yet been described.

Members of any one group within the genus Bacterium in general behave similarly. Each member of the group desensitizes the skin locally toward other members of the same group, but fails as regards members of other groups.

Rough (R) and Smooth (S) variants behave similarly from the allergic standpoint. The predominating one appears to be of the O type which withstands heating to 100° C. for thirty minutes. The thermolabile H-antigen, which is destroyed well below 100° C., is demonstrable in some cultures of *B. coli*, and should be present in greater amounts in the actively motile organisms. Thus far it does not appear that these two types of antigens cross-protect reciprocally. Much more research, however, remains to be done in this field.

Treatment of the so-called normal organisms of the intestine with soricin incapacitates them to react intradermally apparently by destroying their antigenic properties.

CONCLUSIONS

The pathogenic Gram positive cocci found in stool culture of asthmatics and other allergic subjects behave as allergens. Their action combines in varying degrees type specificity and species specificity. An outstanding bacterial allergen of the latter nature was reported.

The group specificity of "normal flora" bacteria was studied, and certain properties of the antigens were described.

It is my belief that alterations in the integrity of the colonic mucosa make possible the absorption of products of the ordinary pathogens and likewise of the so-called normal flora. The behavior of the two differs in marked degree, but both must be considered as possible allergic factors in nonseasonal cases.

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THE PROBABLE ETIOLOGY OF POLLINOSIS IN GALLUP, NEW MEXICO*

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THAT pollinosis is very much of a regional problem in many instances, is readily admitted by some workers and as emphatically denied or ignored by others. The latter attitude may in many cases be due to a lack of familiarity with the basic facts in this problem. It must be admitted that large areas in this country are characterized by a botanic flora which is subject to few variations. This fact does not permit one to assume that the entire country is so characterized. For the past three years we have been rather intensively studying this problem as it relates to certain parts of California, Arizona, and New Mexico.[1-3] This section has at least one factor in common, namely, semiarid climate. This alone would not necessarily make for a universal similarity in hay fever producing plants. Not only may the number and variety of plants differ enormously in the several areas within this territory, but the season of pollination may likewise vary as much. This will be especially emphasized in succeeding paragraphs. A profile map of the areas we have studied indicates a definite increase in altitude as one progresses eastward from a low point of 483 feet at Needles, California, to an altitude of 6,505 feet at Gallup, New Mexico, the object of our present survey. This community is located about 29 miles west of the continental divide. Gallup has a population of 6,000 and is the county seat of McKinley County. It is undoubtedly the most important town in northwest New Mexico, and serves as a center of supplies not only for the coal mines near by but also for the region within a radius of 50 miles or more, including part of the Navajo Indian Reservation, to the north, and the Zuni Pueblo, to the south.

The importance of this section was early appreciated, as it was a station on the old pony express and is now served by the National Old Trails Highway and is a division point for the Sante Fe Railroad. The Puerco River bed is found in the center of the valley and the highway and railroad run parallel with it for many miles. The soil here in this valley is of the Mancos shale and a few miles east runs the Nutria monocline, an outeropping of pink sandstone known locally as the "Hogback," which is a part of the mesaverde formation.

The climate of Gallup, New Mexico, in common with that of the various communities we have studied, is semiarid in character. In the

*From the Allergy Clinic, Santa Fe Coast Lines Hospital Association.

summer the days are usually hot, although tempered by cooling breezes, and the nights are generally cool and pleasant. In winter the nights are very cool but the days are generally sunny and warm. No climatological data are available for the town itself but the observations at the weather bureau station located at the Gamerco coal mine, about three miles north of the center of town, are a satisfactory representation of the conditions in Gallup. These data have been placed at our disposal by the New Mexico section of the Weather Bureau, U. S. Department of Agriculture, and are represented in Table I.

TABLE I

WEATHER REPORTS FOR GAMERCO, ARIZONA

	AVERAGE TEMPERATURE IN DEGREES F.		PRECIPITATION IN INCHES		DATES OF LAST AND FIRST KILLING FROST	
	1931	1932	1931	1932	1931	1932
Jan.	26.0	19.4	0.62	0.97		
Feb.	34.8	34.5	1.36	1.49		
Mar.	37.5	38.0	1.16	1.40		
Apr.	48.5	46.0	1.04	0.97		
May	54.0	55.0	0.91	1.09	May 19	May 7
June	65.2	62.7	1.01	0.59		
July	70.8	69.0	1.92	2.05		
Aug.	68.2	68.2	1.72	1.64		
Sept.	63.2	59.4	2.64	0.49		
Oct.	51.2	47.9	1.05	0.31	October 11	October 4
Nov.	32.6	39.0	3.47	0.00		
Dec.	19.4	22.2	0.95	0.78		
Annual	47.6	43.7	17.92	11.73		
Highest	94	92				
Lowest	−17	−13				

The annual rainfall over a long period of time averages approximately 14 inches and is fairly well distributed over the twelve months of the year. We shall attempt to show that the dryness of the climate is expressed in the vegetation.

In this survey the schemes previously outlined[1-3] were followed. A preliminary survey was made in order to become acquainted with the general topography as well as with the type and abundance of vegetation. The actual survey involved three visits; namely, May and August, 1931, and August, 1932, and a rather detailed study of the section over this period of approximately one and one-half years. The sampling stations were located at widely separated points in an effort to sample fairly the vegetation of this region. The topography here, in contrast to the plateau of the Holbrook-Winslow section for example, makes this feature especially important, even though the area is but a few miles in extent. The panorama of this community, taken from a hill to the northwest and considerably higher than the town, shows to some extent this variation in topography. The approximate locations of the sampling stations have been indicated.

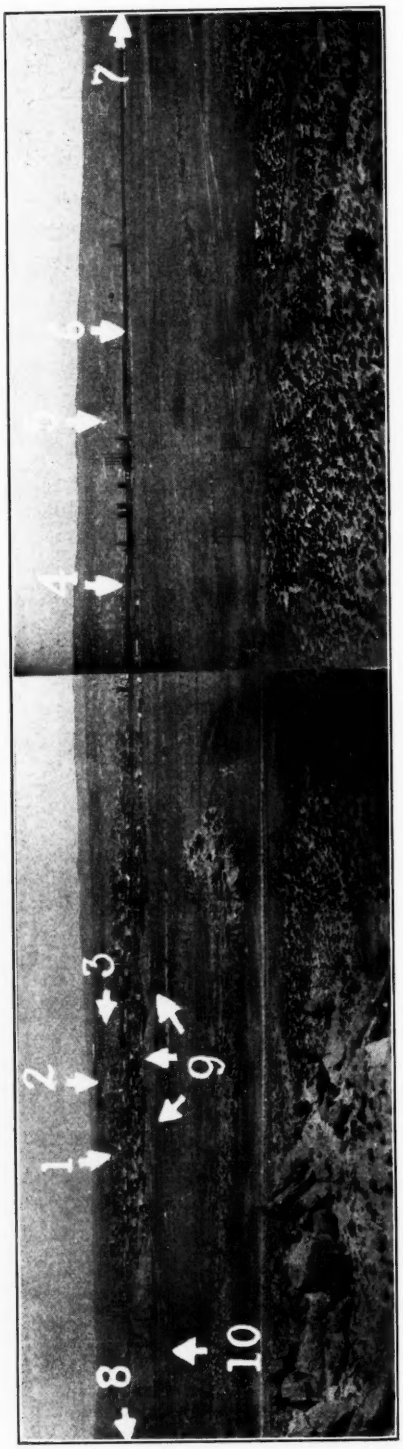

Fig. 1.—Panorama of Gallup, New Mexico, taken from a hill northwest of the town.

Station 1, directly south of and considerably higher than the railroad station and near the most remote house from town, has a vegetation composed of *Salsola pestifer*,[4] which is especially common in the spring;

Fig. 2.—*Chenopodium watsoni.*

Fig. 3.—The *Artemisia tridentata—Juniperus monosperma* formation. Note the abundance of *Juniperus* on the higher places and its absence on the valley floor.

Hilaria jamesii, the most common grass; *Chenopodium watsoni* (Fig. 2), frequent; *Atriplex canescens*, few; *Juniperus monosperma*, fairly common; and *Chrysothamnus greenei*, also rather common.

Fig. 4.—Habit of *Artemisia tridentata*. Note the four-foot marker in this and several other photographs.

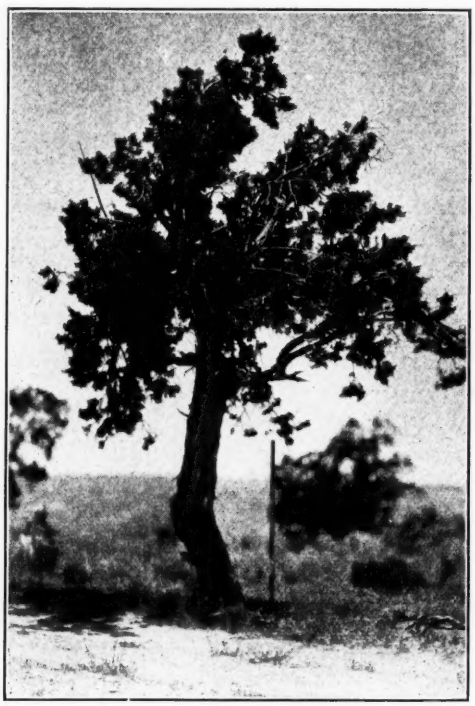

Fig. 5.—*Juniperus monosperma*.

Station 2 (Fig. 3) is on the top of a large mesa several hundred feet above the floor of the valley. Here *Artemisia tridentata* (Fig. 4) is probably the most abundant plant, with *Salsola pestifer*, occurring a little more abundantly than at Station 1. The trees, *Juniperus mono-*

Fig. 6.—*Juniperus monosperma*, fruiting branch.

Fig. 7.—*Pinus edulis*, staminate cones.

sperma and *Pinus edulis*, are somewhat irregular in their distribution. *Hilaria jamesii* is the common grass.

Station 3 is one mile southeast of the railroad station, on a hill near the town reservoir, about one-half mile south of the golf course. The vegetation at this station is a little more dense than that at Station 1. *Salsola pestifer* and *Artemisia tridentata* are abundant codominants, but *Juniperus monosperma* (Figs. 5 and 6) is very common and also *Pinus*

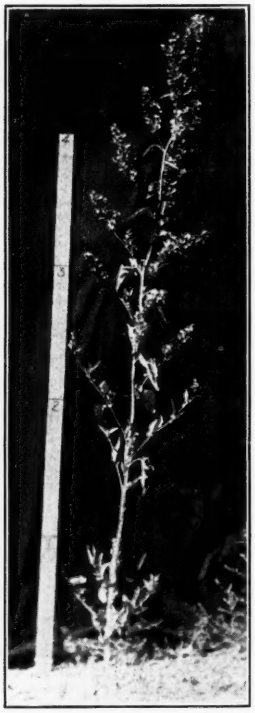

Fig. 8.—*Atriplex hastata.*

Fig. 9.—*Atriplex hastata,* showing the detail of fruiting bracts and leaves.

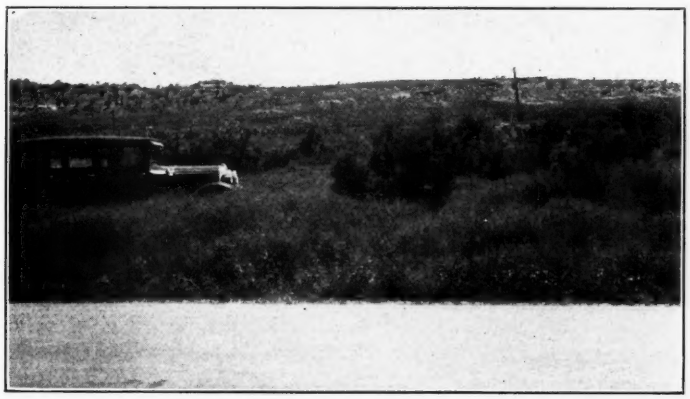

Fig. 10.—Station 7 with *Sa'sola pestifer* very abundant along the highway and so tall as practically to obscure the lower half of the automobile. *Sarcobatus vermiculatus* in the background and many *Juniperus monosperma* on the hills in the distance.

Fig. 11.—*Sarcobatus vermiculatus*, habit view.

edulis (Fig. 7). Of the grasses *Bouteloua gracilis* and *Hilaria jamesii* are of equal importance. Four other plants, *Atriplex hastata* (Figs. 8 and 9), *Chenopodium watsoni*, *C. album*, and *C. leptophyllum*, are found at this location, but none is very abundant.

Station 4 is on Zuni Road, about one-half mile from town. Here *Salsola pestifer* is very common, and *Hilaria jamesii* and *Agropyron palmeri* are fairly so. Numerous species of Chenopodiaceae are present but none is very common. In August, 1931, the physiognomy of this area was dominated by a luxuriant growth of *Cleome serrulata* (Bee plant) which is commonly assumed by lay persons to be a factor in hay fever. On the identical date one year later there was none to be found.

Station 5, one mile farther south up the Zuni Road, presents a similar picture of *Salsola pestifer* abundance, but *Artemisia tridentata* has already become fairly common and the *Juniperus monosperma* is seen on the hills near by. *Hilaria jamesii* is the common grass and *Hordeum jubatum* is secondary.

Fig. 12.—Staminate inflorescence of *Sarcobatus vermiculatus.*

Station 6 is a mile west of town on the valley floor and comprises an area on each side of the highway. The family Chenopodiaceae dominates the vegetation of this area and has the following abundance: *Atriplex powellii,* very common; *A. canescens,* common; *A. rosea,* fairly so; and *Salsola pestifer,* common along the highway. At one of the three observations *Cleome serrulata* was especially conspicuous.

Station 7 (Fig. 10), three and one-half miles west of town, along the highway, is also characterized by Chenopodiaceae. The most abundant is *Salsola pestifer,* but *Sarcobatus vermiculatus* (Figs. 11 and 12) has become quite common. The important atriplexes are *A. caput-medusae* (Fig. 13) and *A. powellii* (Figs. 14 and 15).

Station 8, a mile east of town is marked by the appearance of *Juniperus monosperma* and the dominance of *Artemisia tridentata. Salsola pestifer* is likewise prominent in this area.

Station 9, the residential section, has some ornamental trees, such as *Tamarix gallica, Robinia pseudacacia,* and *Populus fremontii,* which is the common shade tree throughout the town. Lawns are very rare and practically the only grasses are those native to the section. Of the ruderals, *Salsola pestifer* is the dominant, but *Amaranthus retroflexus* and *Xanthium commune* are both common. *Kochia americana* (Fig. 16)

Fig. 13.—*Atriplex caput-medusae,* showing the characteristic pistillate bracts.

was found only in a small section of the town, but *Kochia scoparia,* the cultivated variety, is quite common and often escapes cultivation.

Station 10, north of town, part way up the slope on the road to the large coal mines, also reveals a dominance of *Salsola pestifer; Sarcobatus vermiculatus* is common in this section and *Artemisia tridentata* becomes fairly so, especially with increasing altitude.

In the previous descriptions of sampling stations we have tried to confine our remarks to the most important plants. In Table II, all

Fig. 14.—*Atriplex powellii*, habit.

Fig. 15.—*Atriplex powellii*, showing staminate flowers at the left and the pistillate flowers in the axils on the leaves on the right.

plants identified at each station are indicated. We do not wish to convey the impression in this or any other survey that each is of necessity a hay fever producing plant, but they are included in the table in order to make more complete the study of each part of the com-

munity. The common names are given, as they may be of some value to one unfamiliar with botanic terminology. We have by no means exhausted these terms, but have tried to select the ones most widely used.

A study of Table II reveals first of all the significance of *Salsola pestifer* at each sampling station and hence of the entire area. The next most important from the standpoint of distribution is one of the Compositae, *Artemisia tridentata*. If one should compare these findings with those of Winslow-Holbrook, an important change in botanic emphasis would be evident. In that survey the Chenopodiaceae dominates; in this of Gallup a single member of the family, *Salsola pesti-*

Fig. 16.—*Kochia americana*.

fer, is the most significant plant, yet representatives of the remaining genera occupy a relatively minor position. From the standpoint of distribution also the Graminae and Compositae challenge the Chenopodiaceae for the position of prime importance.

In view of the fact that we have placed so much stress on the Chenopodiaceae we wish to call attention to the fact that several species not previously emphasized are herein noted and in some cases photographic representations are presented. The most notable examples of these are *Atriplex caput-medusae*, *Chenopodium watsoni*, *Kochia americana*, and *Sarcobatus vermiculatus*. The last mentioned, however, was found in Holbrook. The complete absence, so far as we are able to determine, of some of the Chenopodiaceae important in one of

TABLE II

BOTANIC SUMMARY OF GALLUP, NEW MEXICO

SCIENTIFIC NAME	COMMON NAME	STATIONS 1	2	3	4	5	6	7	8	9	10	SEASON OF POLLINATION
CUPRESSACEAE	CYPRESS FAMILY											
Juniperus monosperma	One-seeded juniper	**	**	****	–	**	–	–	**	–	**	Early Sp.
PINACEAE	PINE FAMILY											
Pinus edulis	Pinyon pine	**	**	***	–	–	–	–	–	–	–	Early Sp.
GRAMINEAE	GRASS FAMILY											
Agropyron palmeri		–	–	–	***	**	–	–	–	–	–	Sp.
Aristida fendleriana	Fendler's aristida	–	**	–	–	–	–	–	–	–	–	Sp.
Bouteloua gracilis	Blue grama	**	**	***	–	**	–	–	–	–	–	Sp.
Bromus polyanthus	Great basin brome grass	–	**	–	–	–	–	–	–	–	–	Sp.
Chaetochloa glauca	Pigeon grass	–	–	–	–	–	–	**	–	–	–	Sm.
Echinochloa crusgalli var. *zelayensis*	Mexican barnyard grass	–	–	–	**	–	–	*	–	–	–	Sm.
Hilaria jamesii	James' galleta	***	***	***	***	***	–	–	–	–	–	Sp.
Holcus halepensis	Johnson grass	–	–	–	**	–	–	–	–	–	–	Sm.
Hordeum caespitosum	Tufted barley	–	–	–	*	–	–	–	–	**	–	Sp.
Hordeum jubatum	Squirrel tail	***	–	–	–	**	***	**	–	***	–	Sp.
Panicum berbipulvinatum	Western witch-grass	–	–	–	–	–	–	**	–	–	–	Sm. Fl.
Oryzopsis hymenioides	Indian mountain rice	*	–	–	–	–	–	–	–	–	**	Sp.
Poa sp.		–	**	–	–	–	–	–	–	–	–	Sp.
SALICACEAE	WILLOW FAMILY											
Populus alba	White cottonwood	–	–	–	–	–	–	–	–	**	–	Early Sp.
Populus wislizeni	Valley cottonwood	–	–	–	–	–	–	–	–	***	–	Early Sp.

* = present or rare.
** = fairly common, few.
*** = common.
**** = very common or abundant.

– = does not occur.
Fl. = pollinates in the fall.
Sp. = pollinates in the spring.
Sm. = pollinates in the summer.

TABLE II—CONT'D

SCIENTIFIC NAME	COMMON NAME	STATIONS 1	2	3	4	5	6	7	8	9	10	SEASON OF POLLINATION
POLYGONACEAE	BUCKWHEAT FAMILY											
Eriogonum sp.		**	–	**	–	–	–	–	–	–	–	Sm.
Polygonum sp.	Knotweed	–	–	–	–	–	–	**	–	–	–	Sp.
CHENOPODIACEAE	SALTBUSH FAMILY											
Atriplex canescens	Shad-scale	**	–	–	***	**	***	–	–	**	–	Early Sp.
Atriplex caput-medusae		–	–	–	–	–	–	***	–	–	–	Sm.
Atriplex hastata	Fat-hen	–	–	**	–	–	–	–	–	–	–	Sm.
Atriplex powellii		–	–	–	–	–	****	***	–	–	–	Sm.
Atriplex rosea	Red orache	–	–	–	*	–	**	–	–	**	***	Sm.
Chenopodium album	Lamb's-quarters	–	–	**	**	**	**	**	–	***	–	Sm.
Chenopodium leptophyllum		**	–	***	–	–	–	–	–	–	–	Sm. Fl.
Chenopodium watsoni		***	*	**	**	**	–	–	–	–	–	Fl.
Eurotia lanata	Winter fat	*	*	–	–	–	–	–	–	–	–	Sm.
Kochia americana	Red sage	–	–	–	–	–	–	–	–	**	–	Sm.
Kochia scoparia	Firebush	–	–	–	–	–	–	–	–	***	–	Sm.
Salsola pestifer	Russian thistle	***	****	***	****	****	****	****	***	***	****	Sm.
Sarcobatus vermiculatus	Black greasewood	–	–	–	–	–	***	***	–	–	***	Sm.
AMARANTHACEAE	PIGWEED FAMILY											
Amaranthus blitoides		–	**	–	–	–	**	**	–	**	–	Sm.
Amaranthus retroflexus		–	–	–	**	–	**	–	–	***	–	Sm.
CAPPARIDACEAE	CAPER FAMILY											
Cleome serrulata	Rocky mountain bee plant	–	–	–	***	–	****	**	***	***	**	Sm. Fl.
ROSACEAE	ROSE FAMILY											
Coxania stansburiana	Cliff rose	–	***	–	–	–	–	–	–	–	–	Sp.

TABLE II—CONT'D

SCIENTIFIC NAME	COMMON NAME	STATIONS 1	2	3	4	5	6	7	8	9	10	SEASON OF POLLINATION
LEGUMINOSAE	PEA FAMILY											
Robinia pseudacacia	Black locust	–	–	–	–	–	–	–	–	**	–	Sp.
TAMARICACEAE	TAMARISK FAMILY											
Tamarix gallica	Salt cedar	–	–	–	–	–	–	–	–	**	–	Sp.
OLEACEAE	ASH FAMILY											
Fraxinus cuspidata	Flowering ash	–	**	–	–	–	–	–	–	–	–	Sp.
LABIATAE	MINT FAMILY											
Marrubium vulgare	Common horehound	–	–	–	**	–	–	–	–	–	–	Sp.
SOLANACEAE	NIGHTSHADE FAMILY											
Lycium pallidum	Rabbit thorn	–	–	–	–	–	–	–	***	–	–	Early Sm.
COMPOSITAE	SUNFLOWER FAMILY											
Artemisia tridentata	Sagebrush	–	****	****	**	–	*	–	****	–	***	Late Fl.
Chrysothamnus greenei	Rabbit brush	***	–	–	**	**	–	–	–	–	–	Late Fl.
Erigeron sp.	Fleabane	–	**	–	–	**	–	–	–	–	–	Sm.
Franseria tenuifolia	False ragweed	–	–	–	–	–	–	*	–	–	–	Fl.
Grindelia sp.	Gum plant	–	–	–	–	–	*	–	–	**	–	Fl.
Gutierrezia sarothrae	Matchweed	–	–	*	–	–	–	–	–	–	–	Sm.
Helianthus annuus	Common sunflower	–	–	–	–	–	–	***	–	**	*	Sm.
Xanthium commune	Cocklebur	–	–	–	–	–	–	–	–	***	–	Sm.

the following communities, Needles, Calif., Seligman, Winslow and Holbrook, Arizona, should be noted.

The grass problem here possibly occupies a position equal to that in Winslow-Holbrook, but the species differ considerably. In the latter community *Cynodon dactylon*, *Distichlis spicata*, and *Sporobolus airoides* which were emphasized at numerous sampling stations, are apparently completely absent from the Gallup section.

Here, as in no other community we have reported, the woodland association, *Juniperus* and *Pinus*, is a potential factor in clinical allergy. The other trees that may be considered are in the main limited to the town area, and consist chiefly of cottonwoods, locust, and tamarisk. In the three preceding surveys members of the family Compositae have been of little importance. In this report we have already called attention, in the preceding paragraphs and cuts, to the prominent place occupied by *Artemisia tridentata* and we have qualified most of our statements by emphasizing distribution rather than the importance in pollinosis. This species is an outstanding example of the possible need for such qualifications. In spite of the fact that the plant is widely distributed, especially on the higher levels in this section, we have been unable to find it pollinating even in late summer or early fall. A specimen obtained in mid-September, after onset of cold and possibly frosty nights, was found to be nearly ready to blossom. It would appear therefore that distribution is a minor factor in determining the significance of this species in pollinosis. Should all of it pollinate at this date its period of viability would undoubtedly be very short.

In the opening paragraphs we called attention to the possible regional problem of pollinosis, and probably at no place better than at Gallup may this be demonstrated. The variation of elevation from the center of the community to points but a mile or so distant to the north or south reflects a greater change of vegetation than may be found in hundreds of miles in certain sections of the country. Here, interestingly enough, *Salsola pestifer* has maintained an important position at all stations. A few others have emphasized the changing character of semiarid vegetation and that observations made one year may not necessarily apply to the next. We have kept this fact in mind and have distributed the time of our observations so as to avoid, so far as possible, this error. We have cited herein one striking illustration of such annual variation. We refer to the "showy" *Cleome serrulata* which was so conspicuous at several stations one season and could not be found at all on the identical date the subsequent year. Although this has been used as an example, we do not subscribe to the lay belief that the plant is of importance in hay fever. This fallacy probably arises from the fact that it blossoms at the same time

as the hay fever ones. What has been said of this is quite likely to be true of *Helianthus annuus*.

The early spring season in Gallup is undoubtedly related to the pollination of *Juniperus monosperma* and *Pinus edulis*. The mid-spring season is probably of little importance and our extensive observations would lead us to minimize the importance of the grasses until some time subsequent to May 15. We have considerable evidence to indicate that *Salsola pestifer* here begins to be important about that season. This is in marked contrast to our findings, but a few days earlier, at Seligman. *Salsola kali* there was very immature and the other Chenopodiaceae were so undeveloped as to make their identification practically impossible. This is especially interesting in view of the fact that Gallup is at a higher elevation and one would ordinarily expect the season here to be later than at Seligman. Between the last week of May and the first of August the Chenopodiaceae reached the height of development and many had ceased pollination before the latter date.

We have already referred to the late fall season of pollination of *Artemisia tridentata* which tends to minimize the importance of this plant, and other Compositae are so scattered or infrequent as to merit but little consideration.

CONCLUSIONS

1. The community represented by this study has an altitude of 6,500 feet, and an average annual rainfall of 14 inches. The climatic conditions are such that the major growing period for most botanic species is between May 15 and October 5.

2. Distribution of botanic species varies widely in but short distances from the center of town. The significance of this has been emphasized. Conspicuous annual variations have likewise been demonstrated.

3. The potential importance of *Juniperus-Pinus* association in early spring pollinosis has been emphasized.

4. Grasses may be a factor due to their abundance. The botanic types are quite distinct from those important in several other semiarid areas.

5. The Chenopodiaceae, which dominates many desert sections, are of possible secondary importance with respect to distribution. Several species of importance here, but not especially emphasized at other points, are described.

6. The widely distributed sagebrush, *Artemisia tridentata*, is cited as an example of the major importance of date of pollination as compared to occurrence of species.

7. The season, during which certain of the Chenopodiaceae may be factors in hay fever, is much earlier than in some areas at a much lower altitude.

8. Additional evidence relative to the regional problem of pollinosis is presented.

We wish to acknowledge our deep indebtedness to Mr. Phil Curto and his assistant, Mr. G. F. Tanguy, whose aid has been invaluable in the field work. As in previous surveys, the panoramas and photographs of plants were made by Mr. I. F. Craig, of Needles, Calif.

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MINOR ALLERGY: ITS DISTRIBUTION, CLINICAL ASPECTS AND SIGNIFICANCE*

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IT APPEARS to be quite generally agreed that from 7 per cent to 10 per cent of the population at large suffers from manifest allergic disease. The lower figure is that preferred by those who at the time of their surveys limited unquestioned allergy to asthma, hay fever and urticaria. The higher is that accepted by those who recognize an allergic etiology in certain cases of other diseases, particularly eczema and migraine.

I have for several years in the course of my practice in general internal medicine, been struck by the observation that a very large number of persons who would be classed as nonallergics, will, on questioning, recall a transient minor allergic manifestation in their past experience. This has occurred so frequently that I have made the statement that if we were to include transient minor allergic manifestations, usually not pronounced enough to require medical advice, the percentage of allergic individuals would probably reach more nearly 40.

In the summer of 1932 we undertook a preliminary survey of 100 so-called nonallergic individuals.[1] This included persons who denied being subject to or having had treatment for asthma, hay fever, urticaria or eczema. The number of this 100 who on questioning recalled having had transient allergic manifestations, not sufficiently prolonged or repeated to require medical consultation was surprising. Sixty-one of the 100 had at some time experienced one or another evanescent allergic manifestation. Twenty-nine had had urticaria, 6 eczema, 1 hay fever, 3 asthma, 15 sick headaches, and 47 indigestion. The next point of interest which developed in this series was best exemplified in the cases with indigestion and sick headaches attributable to allergic causes. Almost without exception the individual could name the food responsible for symptoms, and, again, almost without exception the responsible food was one which was eaten only occasionally. Of the 100 in the survey, 32 had had recurrent headaches, and of these 15 attributed them to specific foods, the avoidance of which had relieved the headaches.

The 47 with history of indigestion described their symptoms variably as diarrhea, nausea, vomiting, cramps, gas, belching, heartburn, palpitation, sore mouth and sour stomach. Without exception they were able to name the responsible food, foods eaten only occasionally.

*Read before the Eleventh Annual Meeting of the Association for the Study of Allergy, Milwaukee, Wis., June 12 and 13, 1933.

Due to this fact, they had spontaneously avoided these foods, thereby curing themselves and avoiding the necessity for medical consultation.

Of the 100 persons 37 admitted having had attacks of hyperesthetic rhinitis. None but an allergic seems to be able to sneeze from six to twelve times in succession and appear even to enjoy it. Here again the cause was recognized by the patient himself in nearly every case, and such as the following were recorded: getting out of bed, sudden chilling, wind, intense sunlight, soap powders, dust, drinking whiskey, beer, pollen, taking aspirin, eating chocolate, perfume, tobacco smoke, molds, odor of fresh paint.

Fourteen of the 100 appear to be examples of contact allergy, attributing their symptoms to wool in 9 cases, soap in 2, and rayon, hollyhock and weeds in 1 each.

Summarizing the entire series, there was evidence of food allergy in 46, inhalant allergy in 14, contact allergy in 14, physical allergy in 9, and drug allergy in 5.

I have emphasized in the preceding discussion that in the vast majority of instances the individual was able to name the offending food or other allergen. This is important, since, from my study, I am led to conclude that this is the most important factor in the separation of the allergic individuals into two groups: the frank or major allergic and the minor allergic. We might also term them the unfortunate allergic and the fortunate allergic. The unfortunate allergic is the individual who has had the misfortune of becoming sensitized to a food with which he comes into frequent or daily contact or a substance, food or otherwise, which he is unable to identify. This group makes up the 7 to 10 per cent of the population who are frankly allergic. The fortunate allergic is he who has had the good fortune to become sensitized to something with which he comes into only occasional contact. He therefore has no difficulty in recognizing the cause of his symptoms, and if avoidance is easy he cures himself. He swells the group of what I have termed the minor allergics. They are allergic in that they have demonstrated their ability to become sensitized, but allergy always remains a minor problem with them.

A COMMUNITY SURVEY

In the belief that a survey of a larger number would justify more definite conclusions we next undertook an allergic census of an entire community. The village of Clover in southern Virginia with a population of 251 was selected for a house-to-house canvass. A sufficient number of additional individuals in neighboring communities was interviewed to bring the entire number for this second survey to 508. The information was obtained by Miss Virginia Gregory, a trained social investigator who carried out her part of the work entirely independently of our own previous investigation.

This second investigation, comprising as it did an entire community would, obviously, include at the same time all frank or major allergies. This is fortunate since it serves as a check on our own interpretation of the information acquired. Without this there would have been no basis for comparison with preceding surveys of the incidence of frank allergy. Among the 508, 55 or 10.8 per cent were promptly recognized as being victims of frank or major allergy. This shows a close correspondence to the generally accepted figure of 7 per cent to 10 per cent and thereby gives justification to our conclusion regarding the remaining 90 per cent. Of the latter, 48.1 per cent presented evidence of minor allergic manifestation at one time or another in their past history and 31.3 per cent gave no such evidence. The remaining 50 or 9.8 per cent are questionable. That is, the history as obtained is suggestive of an allergic reaction but not unquestionably. To avoid hyperenthusiasm in the subject under investigation we have classed the questionable cases as nonallergic, and they will hereafter appear so in this presentation. Even without them the figures are sufficiently astonishing when we realize that approximately 60 per cent of the entire population manifest clinical allergy at one time or another.

An analysis of the series brings out some most interesting observations. Of those major and minor allergics who were able to attribute their symptoms to definite causes, 62.6 per cent were sensitive to foods, 23 per cent to inhalants and 14.4 per cent to contact allergens. Of the same group 50.7 per cent manifested gastrointestinal symptoms, 47.2 per cent skin lesions, 26.4 per cent nasal symptoms, 9 per cent migraine or recurrent headaches, 6.2 per cent asthma; and there were a few cases of less definite symptomatology, such as recurrent sores in the mouth, recurrent so-called conjunctivitis, and recurrent kidney colic.

The study of the foods responsible for minor allergy and the symptoms caused thereby is instructive. We have already observed[2] in the survey of our first 100 cases that there is a distinct difference in the character of the foods responsible for minor allergy as contrasted with those responsible for major allergy. In major allergy the chief foods in order of importance are wheat, milk, bean, egg and Irish potato. In minor allergy they are cucumber, watermelon, strawberry, tomato, onion and cabbage. In both groups other foods trail off with lesser frequency, as indicated in Table I. It becomes apparent from study of this table that the major allergic or frank allergic is more likely to become sensitized to some food or substance with which he comes into frequent or daily or continued contact, while the minor allergic reacts to an allergen with which he comes into only occasional contact. The latter easily recognizes the offending substance and relieves himself by avoidance while the former cannot do so without the aid of diagnostic allergic study.

TABLE I

SURVEY OF ALLERGENIC FOODS (FIRST SURVEY)

	POSITIVE REACTORS IN MAJOR ALLERGY PER CENT	FOODS BLAMED IN MINOR ALLERGY
Wheat	24.0	0
Rye	3.5	0
Barley	3.5	0
Oat	4.5	0
Rice	2.5	0
Corn	4.0	2
Cocoanut	5.5	0
Pineapple	1.5	2
Onion	6.5	9
Asparagus	5.5	1
Banana	4.5	2
Ginger	2.0	0
Fig		
Buckwheat	2.0	0
Rhubarb		
Walnut	3.0	1
Pecan	0	0
Spinach	5.5	2
Beet	0	0
Swiss chard	2.0	0
Turnip	4.0	3
Cabbage	5.0	8
Sauerkraut		
Cauliflower	3.0	0
Mustard	5.5	0
Radish	2.0	0
Raspberry	3.0	0
Strawberry	0.1	10
Apple	3.5	2
Pear	3.0	0
Almond	4.5	1
Prune	7.0	1
Cherry	7.5	1
Apricot	5.5	0
Peach	5.0	2
Pea	3.0	1
Kidney bean	12.0	2
Peanut	2.5	2
Blackeye pea	4.0	0
Lima bean	6.0	0
Bean (string)	3.5	0
Lentil	4.0	0
Lemon	2.5	0
Grapefruit	3.0	1
Orange	5.0	0
Grape	3.5	0
Cotton seed	6.0	0
Okra	2.0	0
Cocoa	4.0	4
Tea	0.6	0
Celery	8.0	0
Carrot	3.0	0
Parsnip	4.0	0
Parsley	0	0
Huckleberry		1
Olive		
Sweet potato	1.5	1
Tomato	7.0	10
Pepper	0.6	3
Potato	9.5	0

TABLE I—CONT'D

	POSITIVE REACTORS IN MAJOR ALLERGY PER CENT	FOODS BLAMED IN MINOR ALLERGY
Egg plant	7.0	0
Coffee	7.0	0
Pumpkin	0	1
Squash	3.5	1
Cantaloupe	5.0	7
Pickles		
Cucumber	2.5	13
Watermelon	0	13
Lettuce	3.5	0
Animal Foods		
Beef	2.0	0
Veal	2.0	1
Milk	14.0	1
Buttermilk		
Butter		
Cheese		1
Egg	9.5	1
Chicken	3.4	0
Pork	1.0	2
Lamb	3.0	0
Sea Foods		
Clam		1
Shrimp		1
Oyster		
Crab		
Lobster		1
Fish		2
Herring		1
Sardine		1
Caviar		
Anchovies		
Miscellaneous		
Whisky		1
Sweets		3
Acids		2
Meats		3
Condiments		1
Mayonnaise		1
Fruits		1
Brains		0
Tongue		0

The order in which the vegetable foods appear follows the botanical or genetic classification.

Table II records the offending foods designated by the 244 minor allergies in this survey together with the symptoms produced. Here again the infrequency with which symptoms attributed to staple foods such as wheat, milk, egg, beef and coffee is noteworthy.

The symptoms described are of great variety and might be attributed to a variety of organic gastrointestinal lesions, but the point which should be emphasized and which justifies the conclusion of an allergic etiology is that the patient himself finds that only a single food or a

TABLE II

FOODS RESPONSIBLE FOR MINOR ALLERGIC SYMPTOMS (SECOND SURVEY)

FOODS	NAUSEA	VOMITING	HEARTBURN*	BELCHING	GAS	CRAMPS	COLITIS	DIARRHEA	HIVES	ITCHING	RASH	HEADACHE	CHEST PAINS	CHOKING	TASTE	TOTAL
	TIMES MENTIONED															
Spinach	1				1	1						1				4
Beet	1	1									1					3
Radish															1	1
Turnip			2	2		1									2	7
Cabbage	12	5	15	31	3	19	1	2			1	9		3	32	133
Strawberry	2	1	3				3	1	20	2	8	2	1		2	45
Apple	1	1	5	1	2	4	2	1	1				1		1	20
Pear			2									1		1		4
Cherry	1						2	1		1						5
Peach			1						1	1	1	1				5
Pea	2	2	5		1	1									1	12
Peanut	2					1						2			2	7
Blackeye pea	1			1	1	1										4
Bean	4	3	3		3	1		3							1	18
Lemon	1		1													2
Grapefruit	2					1			1							4
Orange	1		1			1								1		4
Grape					1										2	3
Cocoa	3	1							1		1				1	7
Carrot															1	1
Sweet potato			1												1	2
Tomato			2			1			49	3	25					80
Potato	2			2	3	1	3					2		1	1	15
Pepper			1													1
Squash	2				1	1		1								5
Cantaloupe	3	1	3	5		5			1		2				3	23
Watermelon	6		5	8	4	3	2					13			4	45
Cucumber	5	1	5	17	5	17					1	2	1		14	68
Pickle	1		2	1	1	1								1	1	8
Lettuce	1		1	1	1	1										5
Oat													1			1
Corn		1	1			1	1	1								5

*Heart-burn—"Sour Stomach—Acid Stomach."

TABLE II—CONT'D

FOODS	NAUSEA	VOMITING	HEARTBURN*	BELCHING	GAS	CRAMPS	COLITIS	DIARRHEA	HIVES	ITCHING	RASH	HEADACHE	CHEST PAINS	CHOKING	TASTE	TOTAL
	TIMES MENTIONED															
Cocoanut	1	1		1		1									1	5
Pineapple												1				1
Onion	14	11	7	13	3	13	2					13	1	3	24	104
Mulberry											1					1
Banana			1	1	2	2			1					3	4	14
Beef	1			1	1	2	1							1		7
Veal	1		1	2		1	1	1					1			8
Milk	1		1		1							2			1	6
Buttermilk			1													1
Casein	2	1	1	1	1	2							1	1	1	11
Egg	3	2		1	1		1		2				1	1	1	13
Chicken		1	1													2
Pork		1	4	1	2	5			4			3	1		2	23
Bacon			1													1
Ham	1		2		1	3				1			2		1	11
Lamb					1	2	1								1	5
"Sea foods"	3	4	4	1	1										2	15
Crab	3	2														5
Herring	1	1				1										3
Lobster	2	1		1												4
Oyster	2			1	1	1										5
Sardine									1							1
Shrimp	1															1
Miscellaneous																
Brunswick stew	3	1		1		1		1				1				8
Fruit			1													1
Ice cream						1	1									2
Liver	1		1				1				1					4
Pie								1								1
Sweets		1	1					1								3
Salad greens		1	1				1								1	4
Sausage	1	1		2												4
Mayonnaise	3		2					1			1					7

*Heart-burn—"Sour Stomach—Acid Stomach."

few certain foods produce the symptoms and that he can eat others with impunity. These are cases of food idiosyncrasy. The first eight columns bring out that symptoms may be referable to the upper intestinal tract or the lower intestinal tract as is the case in frank allergy. The next four represent the skin and central nervous system, tissues often involved in frank allergy. The last three columns, chest pains, choking, and the phenomenon of continuing to taste the food for twenty-four hours or more after it is eaten, are included, first, because they are symptoms actually described by the patient, and second because the foods incriminated correspond so closely to those chiefly incriminated in the preceding columns that one is tempted to wonder whether allergy is actually responsible for these symptoms.

A few other miscellaneous symptoms were attributed by the patients to food idiosyncrasy. Ulcers in the mouth were attributed one time each to strawberry, peach, cantaloupe, chicken, sea foods and four times to tomato. Recurrent typical gallbladder attacks were attributed once each to blackeye peas, Irish potato, beef and oyster. One patient experienced backache each time she ate strawberries. One patient complained of blurring of the vision after eating apples. One had vertigo from watermelon, one sleeplessness each time she ate tomatoes. Eczema was attributed once each to cherry, peanut and cheese and twice each to strawberry, tomatoes and lamb.

The phenomenon of continuing to taste the food for many hours after it has been eaten bears closer study. It is such an indefinite symptom and so frequently mentioned in clinical medicine that one would be inclined to doubt any allergic connection. It was mentioned as a complaint (Table II) 109 times. Only 10 times was it, however, the only symptom. Ninety-nine times it was mentioned in connection with some other allergic manifestation.

Another interesting observation in Table II is the great variety of foods which may be responsible for allergic symptoms. Almost every food is mentioned one or more times. This has a practical application in connection with major allergy and the so-called elimination diet. Those who would dispense with the preliminary sensitization test and start the patient out on an elimination diet fail to realize that the frank allergic, in addition to being more often sensitive to staples is at the same time sensitive to occasionals, and probably in the same frequency as the minor allergic. But he is less able to discover the offending occasionals because of his more or less persistent symptoms from the staples. It is therefore not enough just to prohibit those foods which from experience have been found to be frequently allergenic. Most major allergics will at the same time require the prohibition of certain occasional foods to which they are sensitive. Unnecessary delay can therefore be avoided by the preliminary application of

the sensitization reaction and the prescription of a strictly individualized trial diet based upon the results of a sensitization test.

Inhalant allergy is also represented in this series of minor allergics. Obviously the individual is often less able to ascribe his symptoms to a specific etiologic inhalant factor. The chief inhalant allergic manifestation was explosions or barrages of sneezing. Some were able only to state that these periods of sneezing occurred only under certain circumstances or in certain environments, such as "while playing golf in the spring," or "out of doors," or "when frying food." But it is surprising (Table III) to observe how often a definite cause could be cited.

TABLE III

SUBSTANCES RESPONSIBLE FOR RESPIRATORY SYMPTOMS IN MINOR ALLERGICS

SUBSTANCE	TIMES MENTIONED	SUBSTANCE	TIMES MENTIONED
Dust	53	On arising from bed	14
House dust	12	Marigold	1
Outdoors	5	Roses	1
Dust outdoors	2	Soap flakes	5
Hay dust	3	Soaps	3
Tobacco dust	3	Shaving soap	1
Threshing grain	1	Washing powder	5
Smoke	1	Orris root	1
Tobacco smoke	1	Crowds	2
Coal gas	1	Movies	1
Ragweed	6	In church	1
Weeds	4	Wheat flour	1
Grasses	7	Feathers	1
Pollen	6	Flax	1
Golf in spring	1	Frying food	1
In fields	3	Cocoa butter	1
Oak	1	Strong light	10
Flowers	1	Heat	1
		Wind	1

Foods responsible for dermal manifestations are indicated in Table II. Atropine was responsible in one case of hives; quinine in one caused attacks of angioneurotic edema. Table IV indicates other substances accused as being responsible for dermal manifestations, presumably acting chiefly as contact allergens. The subject of symptoms from contact with wool is of special interest. Forty-one of the allergic series complained of itching, rash, or hives from contact with wool. Eleven of the questionable cases and 1 of those classed as nonallergic did likewise. Seventy-seven and three-tenths per cent of those complaining of symptoms due to wool were classed as allergic on the basis of related symptoms. Thirteen and seven-tenths per cent of all the allergic cases complained of symptoms due to contact with wool, while only 2 per cent of the nonallergics did so.

The criticism might properly be raised that in this series there may have been a tendency to include as allergic, manifestations which

TABLE IV

CONTACT SUBSTANCES RESPONSIBLE FOR DERMAL MANIFESTATIONS IN MINOR ALLERGICS

SUBSTANCE	SYMPTOM				
	ITCHING	HIVES	RASH	ECZEMA	ANGIONEUROTIC EDEMA (SWELLING)
	Times Mentioned by Patients				
Wheat flour			1		
Wheat		2			
Barley flour	1				
Rice powder			1		
Corn shucks and stalks		10			
Corn fodder		1			
Straw		1			
Hay	1				
Oats	1	2			
Grasses	1		1	1	
Weeds	2	2	3	3	
Scrub oak	1				
Grapevines	4	5	2	1	
Fuzzy vines		1	2		
Zinnia		1			
"Snow on mountain"	2				
Peach skin	1	1			
Vegetable skins	1				
Soaps and soap powders		1	6	1	
Talcum	1				
Face powders				1	
After bath	1				
Wool	27	5	9		
Rabbit hair					1
Rayon	4				
Cause unknown		13		2	

might have been due to other causes. In isolated instances this is entirely possible, but I believe that the error due to this factor is small, since in such a very large proportion the individual has been able to incriminate definite specific substances. There is an additional way in which the accuracy of the survey may be assayed. Allergy may be and often is limited to one system such as the gastrointestinal, the respiratory tract or the skin. But it also often involves more than one system. When two or more systems are involved, there is, then, even less doubt concerning the allergic nature of the symptoms. In this series of 244 minor allergics (Table V) one system alone was involved in 114, while two or more systems were affected in 130 cases. In 164, symptoms were attributed to one variety of allergen, food, inhalant or contactant, but in an additional 80 two or more types of allergens were incriminated. The multiple etiology and polymorphous response observed in this series occur in about the frequency that we would anticipate from our knowledge of major allergy and confirms the conclusions that the statistics are reliable.

It is possible that a survey based upon an exhaustive personal discussion with each patient, together with the indicated sensitization reactions, might show a lower percentage with minor allergy, but I

TABLE V

SYSTEMS INVOLVED	TIMES MENTIONED	
Gastrointestinal, only	49	
Upper respiratory, only	12	
Skin, only	53	116
Nervous, only (headaches)	2	
Gastrointestinal and upper respiratory	22	
Gastrointestinal and skin	34	
Gastrointestinal and nervous (headaches)	14	
Gastrointestinal, nervous and respiratory	6	
Gastrointestinal and lower respiratory	1	
Skin and nervous (headaches)	10	128
Skin, respiratory and gastrointestinal	17	
Skin, nervous and gastrointestinal	9	
Skin and upper respiratory	13	
Respiratory and nervous (headaches)	1	
Renal	1	
ALLERGENS RESPONSIBLE		
Foods only	132	
Inhalants only	15	164
Contactants only	17	
Foods and inhalants	34	
Foods and contactants	28	80
Foods, inhalants and contactants	14	
Inhalants and contactants	4	

do not anticipate that the difference from our findings would be sufficient to invalidate our conclusions. I recognize the hazard involved in attempting to designate as allergic, recurrent headaches and dermatitis, from the patient's general description, but would once again emphasize the importance in this connection, of the patient's ability usually definitely to name the offending agent.

The only comparable survey with which I am acquainted is that reported by Rowe,[6] in which he found in a survey of 400 university students, a personal history of probable allergy in 35 per cent.

AN EXAGGERATED PHYSIOLOGIC RESPONSE

If, as would appear from this survey, well over half the population exhibits some allergic manifestation at one time or another, we must reconstruct our understanding of the phenomenon. The question will then be no longer "why do some of the population become allergic?" but rather "why are not all persons allergic at one time or another?" The phenomenon is no longer exceptional; it is the rule.

As I see it, the difference between the allergic and the so-called nonallergic is not so much qualitative as it is quantitative. In my first series of 100 I reported as strong an hereditary predisposition in those classed as nonallergic, as in those classed as allergic. The nonallergies therefore have inherited the tendency but did not happen to experience recognizable allergic manifestations up to the time of the interrogatory. This does not mean that they never will.

The generally accepted requisite for the production of the anaphylactic state in experimental animals is the introduction of antigen into the circulating blood. The work of Walzer[3] and his associates has demonstrated that in the normal individual food substances are not necessarily digested into their constituent aminoacids before absorption, but appear in the blood in a state so little changed from the original that they can still be identified as such by biologic methods. In the process of digestion, therefore, the phenomenon which we consider prerequisite to the development of the anaphylactic state occurs normally each day. The further disintegration of this circulating allergen is a part of normal physiologic assimilation and elimination. Why some manifest symptoms therefrom while others do not, we cannot as yet say, but it is probably not so much a factor of the chemistry of allergy as of an altered physiology of the liver as suggested by Manwaring[4] or of the vagus autonomic system. This much appears clear to me, that allergy is not so much a pathologic reaction as it is a pathologic exaggeration of a normal physiologic response.

If this be true, why do but 10 per cent develop subacute or chronic symptoms sufficient to require treatment? The following explanation appears reasonable. It depends upon an hypothesis which I believe further experience will confirm, namely, that the *natural tendency in allergy is toward recovery, toward a gradual loss of sensitization.*

We have all seen clear-cut sensitizations disappear in the course of time, to be replaced by new ones. We have seen positive skin reactions become negative, on serial retesting. I have described elsewhere[2] a series of cases manifesting transient allergy. I have observed[5] that in food allergy, provided the patient avoids the offending allergen sufficiently long, he gradually loses his sensitization and can finally ingest the offending allergen without reaction. The average requisite period of avoidance in these series was four and one-half years. There is evidence that, provided contact be discontinued, sensitizations disappear, but that the sensitization tends to persist as long as contact is continued.

Applying these observations to the subject under consideration, it would appear that the 10 per cent become frank allergics because of continued contact with the offending allergen and that the remainder do not, because of the unconscious application of the curative procedure of avoidance. The minor allergic recovers because he is the "fortunate allergic." He had the good luck, and so far as we know it is only luck, to become sensitized to something which he could recognize.

CONCLUSION

Upward of 10 per cent of the population develop major allergic manifestations, usually subacute or chronic in character. Approxi-

mately an additional 50 per cent give a history of minor episodic allergic manifestations in the past.

The latter are usually sensitive to allergens with which they come into only occasional contact while the former, in addition, are sensitized to staple allergens with which they come into frequent, often daily contact.

The difference between the two groups depends chiefly upon the degree and frequency of contact with the offending allergen. Recognition of the allergen depends upon this and determines into which class the individual will fall.

The difference between the allergic and the so-called normal individual is more quantitative than qualitative.

Allergy is not so much a pathologic reaction as it is a pathologic exaggeration of a normal physiologic response.

The natural tendency of the allergic state is toward recovery or loss of sensitization provided avoidance of contact is continued through a sufficiently long period.

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DRINKING WATER AS A CAUSE OF ASTHMA*†

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TUCSON, ARIZONA

IT IS a recognized fact that idiosynerasy to purely chemical substances of a nonprotein nature is of rather frequent occurrence. Sensitization to drugs like acetyl-salicylic acid, quinine, ipecac, codeine, pyramidon, and to arsenic compounds, such as sodium cacodylate and arsphenamine, is not uncommon. But, as far as we have been able to learn by a very careful study of the literature on allergy, and by personal inquiry, chlorine in drinking water has never been suspected nor reported as a cause of any allergic manifestation.

We have recently seen a patient in whom it was proved that drinking water was the cause of asthma and so-called functional colitis. Because of its universal use, we feel that drinking water may be an unrecognized cause of allergic manifestations in a considerable number of patients. We are reporting this case in order to call to the attention of others interested in asthma and allied conditions, this hitherto unconsidered cause, so that they may help to determine by their observation just how important it may ultimately prove to be.

REPORT OF CASE

F. J. U., a man, aged fifty-two years, in whose family or past personal history there is nothing significant except that his mother for years had typical attacks of migraine. At present he has pulmonary tuberculosis, bronchial asthma, and functional colitis. The pulmonary tuberculosis has been present for several years in a more or less stationary condition. The bronchial asthma and bowel disturbance are rather recent developments. X-ray study of the colitis revealed that it was not organic but functional. We suspected that both asthma and colitis were on an allergic basis and would probably be controlled after allergic study and treatment. Skin testing gave several positive reactions, the most important of which was caused by milk. Contact was broken with milk and the other substances to which he was sensitive, and almost at once the patient's asthma and colitis began to improve. The colitis improved to a greater degree than the asthma. He was never entirely free, however, from the symptoms of either. On certain days the asthma particularly would be much worse, although never so severe as before the elimination of milk and

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†From the Tucson Clinic.

the other foods to which he had been shown sensitive. We had excluded any possible air-borne factor by the usual methods. He was put on elimination diets, but no further improvement occurred. We were considering bacterial allergy as a possible cause when we discovered that the asthma was decidedly worse on the days the patient felt feverish and drank more water. Remembering that the water supply of most cities has chlorine added to it, we considered this as a possible cause. The patient was therefore asked to drink excessively of water. His symptoms became worse. We then ordered distilled water exclusively, and in a few hours his chest was clear, all asthmatic symptoms were gone, and the colitis became better than it had been for months. This régime was continued for three days without a return of asthma or colitis. We then arranged with the nurse to put in each glass of water taken one drop of sodium hypochlorite solution. Within half an hour after drinking this chlorine water he was wheezing again. This was repeated and the wheezing continued. On substituting distilled water for chlorine water, the asthma ceased, and he remained free from it. Coincidently the bowel symptoms had subsided. Now the patient has neither asthma nor colitis. The symptoms, however, can be provoked at any time by having the patient drink water with chlorine in it.

COMMENT

It is generally known that the chlorine radical of the sodium hypochlorite is the effective part in making water safe for drinking. The sodium is inert. It, therefore, seems reasonable to believe that it is the chlorine radical which is responsible for the asthma in this case and not the sodium. As further corroboration of this conclusion, this patient salts his food with sodium chloride and can take sodium bicarbonate without untoward effect. It seems possible, in view of this particular experience that chlorine in drinking water may be the cause of persistent residual symptoms in a certain number of allergic cases, not otherwise relieved by our present-day rather exhaustive methods of treatment.

110 South Scott Street

Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

ELEVENTH ANNUAL MEETING, MILWAUKEE, WIS.,
JUNE 12 AND 13, 1933

(CONTINUED)

Drinking Water as a Cause of Asthma. SAMUEL H. WATSON AND (by invitation) CHARLES S. KIBLER, Tuscon, Ariz. (For original article, see page 197.)

DISCUSSION

DR. CHARLES H. EYERMANN, St. Louis.—I should just like to report that it has been our experience to have relieved two individuals of intractable urticaria by the use of distilled water. The control in these instances is, from our standpoint, very good, in that they failed to respond to various types of elimination diets, and in desperation we put them on crystal water and allowed them general diet. One individual who had giant urticaria had a recurrence upon the resumption of the ordinary drinking water. We were never able to determine the offending factor.

DR. E. WOOD PHILLIPS, Phoenix, Ariz.—Last year I saw another Arizona patient whose asthma was caused by substances carried by drinking water. This young man had enjoyed excellent health until he went to work at a small hydroelectric station in the mountains. There he began to have asthma, which in time became so bad that he could hardly do his work. His seizures occurred only at this place. At his home in Phoenix he had no asthma, but he was unwilling to quit his job, with no other in sight.

By the ordinary methods it was found that foods, pollens and dusts could be excluded as causes of his trouble. We found that drinking the water of this station caused him to have asthma, even if he carried the water down to Phoenix, where he was ordinarily free from attacks. Similarly, he was free from asthma at his place of employment so long as he used only water obtained elsewhere.

The water from the station was analyzed, and it seemed to be good. It was not chlorinated. The supply came from a deep well, from which it was pumped up to a tank by a jack pump, automatically controlled and lubricated by oil under gravity pressure. A certain kind of oil was always used, and a little of it got into the water, so that a thin oily film covered the water in the tank.

It was found in the course of the investigation that this patient was also sensitive to aspirin. Apparently he was clinically sensitive to various coal-tar products.

DR. MILTON B. COHEN, Cleveland, Ohio.—I think this is important for those of us who have reports of this kind, because there must be a number of simple chemical substances which we ordiarily do not associate with allergic manifestations which are operative in producing them.

We have not seen chlorine itself producing difficulties of this sort, but recently we have had an opportunity to study two chemists who have asthma, and asthma alone, due to platinum chloride. These chemists worked with a chemical company producing a certain type of absorbing matter used in the making of sulphuric acid, and they have handled in the neighborhood of 1,400 ounces of metallic platinum sprayed as platinum chloride after dissolving it in aqua regia in the last ten or twelve years in one case, and in five or six years in the other. They have no allergy of any other type, and yet both of them have intractable coryza and mild asthmatic symptoms when they come into a building where any of this material has been used.

According to his history one man came into the laboratory one day where they were boiling some aqua regia off platinum under a hood. The hood was open at the bottom perhaps an inch, and the fan was turned off a moment or two and the man promptly had an attack. The plant physician brought the man over to the office and brought me some 1 per cent platinum chloride, the same material they were working with. We sprayed into the room a small amount of platinum chloride from a glass nebulizer. Dr. Rudolph and I, and the doctor in the case were in the room. We experienced no symptoms at all, but within a minute and a half these individuals had marked symptoms of generalized coryza.

Dr. Figley happened to be in the office one day when these men were in, and we attempted to test them intradermally. One man had a most beautiful systemic reaction. The amount of platinum chloride they could have gotten from the little bit sprayed in the room was infinitesimal. One drop of a 1:1,000,000 dilution in the eye produced a swelling.

There must be various chemical substances which we ordinarily consider to be quite harmless to which people can become sensitized. I think we should have more reports of this kind carefully controlled, because it may call attention to other substances which we have overlooked.

Dr. Samuel M. Feinberg, Chicago.—At this point I should like to interject a word of caution in the interpretation of these case reports. So often we see cases of asthma and other types of allergic cases react to nonspecific factors. We know that cases of asthma, hay fever and colitis—allergic colitis—might react to other irritants, nonspecifically, and we have for a long time, of course, regarded these as secondary causes in a nonspecific way.

It is perfectly possible, for example, that chlorine inhaled might produce asthma in an asthma patient who is sensitive to something else. It is perfectly possible that any chemical irritant might produce the same results. I should like to see those cases controlled by experiments with other irritants.

In the case Dr. Kibler recited, the association is even more suspicious because this patient had a colitis which might have been disturbed by chemical means. It might have been allergic in the first place but disturbed by chemical irritants. When we realize how frequently we see a colon upset of any kind, whether allergic or otherwise, irritated during an attack of asthma we can see the possibility of the asthma association there. I do not mean to deny the possibilities Dr. Kibler brought out, but I think we should be a little hesistant in accepting all such case reports at their face value.

DR. FRANCIS M. RACKEMANN, Boston.—May I suggest that when this paper is published the title be changed to include the words "Chlorine in" or "Impurities in Drinking Water." The subject is important, and I am afraid the present title is a little weak.

DR. J. A. RUDOLPH, Cleveland.—I should like to digress a little from this case and should like to add that neither of the two platinum chloride sensitive patients we had gave a positive family or personal history of allergy that could be traced.

I should like to ask Dr. Kibler and Dr. Eyermann whether their patients showed any asthma in the family history. We have reasons to be suspicious that these cases of sensitivity to inorganic substances may be comparable to the sensitivity that we find in the epidermal type of reaction.

The chemist referred to in Dr. Cohen's discussion developed asthma on contact with this inorganic substance. His assistant, after working with the same substance for many years, also came down with asthma. I wonder whether the cases referred to by Drs. Kibler and Eyermann had positive family or personal histories.

DR. ALBERT H. ROWE.—I should like to call attention to an observation I have made on several occasions, and that is probable allergic disturbances due to calcium.

In my milk sensitive patients I very frequently have to give calcium, and in two or three I have had very definite evidence that idiosyncratic reactions have resulted from calcium administered by mouth. In one individual who had gastrointestinal allergy and urticaria, both symptoms seemed to be exaggerated or induced by various types of calcium that I attempted to administer, and they were in comparatively small amounts—just a few grains.

DR. GEORGE L. WALDBOTT, Detroit.—It may be of interest to mention in this connection that I had a patient sensitive to iodized salt. The patient had chronic asthma and was relieved by hyposensitization therapy; but she still had slight attacks until ordinary salt was substituted for iodized salt. The attacks recurred promptly when iodized salt was taken again.

DR. KIBLER.—I should like to say that in Tucson we traced the water supply this patient was getting through the state bacteriologist and found that the water was purified by using liquid chlorine, and this pumping station was within two or three blocks of the patient's home. We were unable to skin test this patient with chlorine because he died rather suddenly from an acute cardiac decompensation.

I shall be very glad to have the title of the paper changed.

On Dr. Piness' question, we found the elimination of milk did not eliminate the asthma. It seemed to help somewhat, but it was not eliminated at all until we substituted distilled water for city water.

This patient had a family history only of migraine in the mother.

The Importance of Adequate Tests and Their Proper Evaluations. ZELLA WHITE STEWART, Iowa City, Ia. (For original article, see page 148.)

DISCUSSION

DR. C. ULYSSES MOORE, Portland, Ore.—Dr. Stewart deserves much credit for bringing to our attention the problem of adequate or full testing, especially of foods. Physicians as a class are inherently thrifty

both for themselves and for their patients. Hence the perennial desire to obtain a short cut in allergy tests. Some years age groups of foods, groups of pollens, etc., were mixed into single extracts and one test per group was done. I was surprised to find this method still in use by certain European allergists in 1930. Recently I learned that some men in this country are using this technic or the equally unsatisfactory method of testing with one food or one pollen from each group.

Let us grant that accurate short cuts would be desirable from many standpoints, but our present ones, as Dr. Stewart has shown, are full of errors and therefore tend to bring allergy into disrepute.

My first work with food allergens began in 1915. The tests then gave such a small percentage of accurate results that the work was discontinued. In 1921 the newer extracting methods were tried and again dropped. By 1925 improved technic made it possible to obtain a sufficiently high percentage of satisfactory results to warrant a proper charge for the tests made and a statement that this laboratory method is comparable with others in accuracy. We now tell our patients frankly that full testing—about two hundred food tests—contains a 10 per cent error, and that less than full testing may or may not give information of value. This protects the science of allergy as applied to foods and at the same time permits a family to have partial testing if their purse demands it. However, does not the publication of partially tested cases deserve the criticism of this organization? Again I wish to thank Dr. Stewart for emphasizing the importance of adequate testing.

An Evaluation of Skin Reactions in Food Sensitive Patients. Albert H. Rowe, Oakland, Calif. (For original article, see page 135.)

DISCUSSION

Dr. George Piness.—Reading the title of Dr. Rowe's interesting paper gave me an idea of what he was going to say. I therefore only wish to quote what Dr. Rowe has said in the past. Quoting Dr. Rowe, from the *Journal of the American Medical Association*, June 20, 1925:

"This paper is based on 234 cases of bronchial asthma in which the patients cooperated satisfactorily in their treatment during the year 1923 and 1924. No cases are reported in which the patients have not cooperated and have not been under observation for a minimum of four months. In cases treated before 1923 the results were not as good as those reported here because of our lack of knowledge of many of the causes of asthma or lack of appreciation of the importance of routine testing and retesting."

Quoting further: "Thus 91 per cent of my patients gave one or more positive skin reactions as contrasted to 48 per cent reported by Walker in 1920, and 85 per cent reported by Cooke in 1922. I feel that this high percentage of positive reactions is due to the use of a large number of foods, animal emanations and pollen proteins, to the use of orris root in routine testing and to the use of many miscellaneous proteins in the unusual case. Retesting on several occasions when asthma remained uncontrolled has revealed many reactions that would have been missed. In this series no positive reactions to bacteria have been recorded. With improvements in methods of preparation of proteins and further discoveries of allergic causes of asthma more positive reactions will probably be obtained."

Quoting again from the same article: "Conclusion: One or more protein sensitization skin test has been found positive in 91 per cent of 234 cases of asthma. Treatment of asthma based on such reactions usually gives satisfactory results if full cooperation of the patient is obtained. Sensitization is usually multiple, inhalants including animal emanation substances, orris root, pollen, and dust are the most frequent causes of asthma. Wheat, eggs, milk, and cereals other than wheat are in order of sequence the most common foods that cause asthma, though any foods may be responsible. Complete or marked relief has been obtained in approximately 90 per cent of the 234 cases of asthma."

Dr. Rowe spoiled my discussion by not including children in this group. He reported previously a series of 110 cases.

Why should it be necessary to do a juggling act with diets when he can get 91 per cent of relief in his series of cases with specific evidence of sensitivity? There is something wrong in the picture. Certainly, allergists have not retrogressed. I think, on the whole, we have been most progressive. I cannot understand the paradox now of Dr. Rowe's inability to get specific reactions with proteins, when he is using perhaps a better protein than the same chemical firm made in 1926, and also the fact that if they did not change the preparation of the protein he should be getting the same amount of reaction and results.

Dr. M. Murray Peshkin.—In 1927 Dr. Fineman and I carried out a study based on 100 allergic patients who were tested by the scratch and intradermal methods with 33 corresponding proteins. The dry powdered extracts employed for the scratch test were prepared by a commercial concern, and the routine fluid extracts for the intradermal tests were kindly furnished by Dr. A. F. Coca. The fluid extracts were also applied with the scratch method when the intradermal test gave a reaction above the control. The conclusion from this study was that one method of testing should not be used to the exclusion of the other. In other words, all available methods of testing should be employed if maximum information is to be obtained.

As a routine procedure and from the standpoint of safety, the scratch test, especially in children, appears to be the method of choice and is the one with which the study is started. When the scratch is negative the intradermal test with undiluted extracts is employed. This practice in the last six years has resulted in only a single mild general reaction. In the absence of a positive intradermal reaction the ophthalmic test may be employed. Only dry powdered natural substances are used for the ophthalmic test. This test is practically restricted to dry pollen because the food and other powders are chemical extracts. The trial and error (elimination) diets, taking into consideration biologically related foods, must also be employed and considered as a means of testing in these patients with suspected food allergy and negative cutaneous tests. These cases, shown in detail by Dr. Rowe, are interesting and common in the experience of all workers.

It can be safely stated that the employment of all methods of testing not only enables the worker to check one method against the other but also permits of a broader vision as to the rôle that tests play in allergy.

Dr. Warren T. Vaughan.—I think there are very few people in this room who will deny we have accomplished a great deal in the study

of allergy through the skin test, and even the skin test as applied to foods. There is no doubt that there is a decided variability.

For a time we were using four different preparations, and we have never yet found entire agreement among all four. As a matter of fact, if you use the same preparation over again you get variation, so much so that if you are not getting anywhere the logical thing to do is to repeat the study, and very often you will find an entirely different type of reactions.

I am going to reverse the viewpoint that Dr. Rowe has presented to you. His viewpoint has been that the elimination diet demonstrates what is causing the trouble, and that the skin test is used just to check up on it or, rather, the skin test is used to check on the accuracy of the elimination diet. Let us grant that the skin test with foods is reliable in only 50 per cent of the cases. If, by a preliminary series of skin testing, as Dr. Rowe suggests, first scratch and then intracutaneous, you find 50 per cent of the offenders, you have gotten off to a mighty good start. That is the logical point of departure to be followed by a strictly individualized dietary program—call it trial diet or elimination diet if you will—in which certain other foods will be discovered which have given false negative skin reactions, which we have not discovered by means of the skin test.

I have recently been over our series trying to evaluate the relative effectiveness of the skin test and the trial diet. The trial diet is never used in our work except with the food diary, and it is really the food diary that gives the answer. The patient is tested, and he eliminates not only the positive foods, but also the borderline foods. Obviously, he is eliminating a lot of foods that are not causing trouble. Then he keeps a food diary, on his restricted diet, and in the course of the weeks of the food diary, in which he has had repeated attacks, other foods show up. Then with the patient relieved, he starts again trying those foods to which he gave positive reactions, and he finds he can take some of them with impunity, and that others are actually causing trouble.

I am going to give you in round numbers (they are almost exactly accurate) our results in this series of 60-odd migraine cases. We found 300 positive reactions. On trial, 150 of those positively reacting foods were actually causing trouble. On the trial diet, and keeping a food diary, 60 additional foods were found to be responsible for trouble.

So with this procedure of preliminary skin testing (which I feel is certainly the point of departure), followed by trial diet and food diary, the relative value of the skin test to foods, and the trial diet is 150 to 60, or 5 to 2, in the relative value of the skin test as compared with the trial diet. The skin test has a value of 5 as compared with the value of 2 for the trial diet, and that is only provided you have done preliminary skin tests.

Dr. Robert L. Benson, Portland, Ore.—I feel that a great deal of our inaccuracy comes from commercial extracts which are not reliable. These fall into two groups, those with false reactions, false positives; and those extracts which are weak, inadequate.

About the time we get a little sample which is good and reacts well, then our 25 milligrams or 50 milligrams give out, and we are looking again for a good extract. The only relief for that is getting a good

supply, if we are dealing with dry extracts, which will last. So I think we shall have either to get somebody to make us a sufficient quantity, or else to make it ourselves, until we have a whole list complete, all of which have been tested, as Dr. Rowe has suggested is necessary, and which will last sufficiently long that we can depend on getting good reactions all the time.

I previously referred to a girl thirteen years old, weighing 56 pounds, who reacted to three-fourths of her known foods. I took her off the whole three-fourths and then watched her weight chart. She gained thirty pounds in a few weeks on one-fourth of her food selected on the basis of these food tests. I could report others.

One lady, who had been off about two-thirds of her food for some time, complained to me and asked if it were not possible now to try some of those foods. I said, "Yes, you can try any one of them you want to. What do you want to try?" She said spinach, orange, and something else. "All right," I said, "try them now." She was in trouble again for the first time in six months. So we tried three others. She was in trouble again, so we just had to give it up.

I believe in getting a list of proteins which are reliable, in sufficient quantities so they will last, and then I believe in most cases they are reliable.

Dr. I. S. Kahn.—I have had the misfortune of a fatality from intradermal food testing, hence my opinion that the indiscriminate use of this method of testing with food extracts is far from harmless. Certainly preliminary dermal tests should be done to obviate trouble, and where positive call for the omission altogether of the intradermal tests of such dermal positives.

Dr. S. J. Parlato.—We have heard so much about negative reactions today that it seems that the pendulum is swinging in the opposite direction to where it was known a few years ago. We were getting too many skin reactions in the past. Now, apparently, we are not getting enough.

I have made an observation which I should like to bring to Dr. Rowe's attention. We all see patients who are commonly known as multiple sensitive. We are confronted with the problem as to what we are going to do with these patients who react to a considerable number of foods. Whether we place them on an elimination diet or trial diet, the main fact is that we are prescribing a very limited diet. Within a week or ten days after eliminating the undesirable foods, we find that the same patient tested in the same way and with the same extracts does not show such a large number of positive reactions. In this way, the patient, himself, apparently has lost some of that hypersensitivity or reactivity of the skin to foods.

Another thing I wish to speak about: food reactions are important only when they are immediately positive. I think that we should be very careful when we speak of delayed positive reactions. My experience is in accordance with Dr. Robert Cooke who states that food reactions are important as etiologic factors only or principally when these are immediate reactions whether by clinical or by skin tests.

In the chart there were quite a number of normal controls which gave positive reactions in the passive transfer test. I wish Dr. Rowe would explain how it is possible to get so many positive controls.

The method of skin testing is also important. If I understood Dr.

Kahn correctly, he said that the intradermal method should be used more widely. As one who uses the intracutaneous method exclusively, I agree with him. If we are going to use the intradermal method to check the results of scratch testing, is it not logical that one should start and finish with the intracutaneous testing? Of course, greater care must be exercised in the interpretation of this test, but with the proper dilution of extracts, as well as a thorough knowledge of their preparation, the interpretation of these tests will not prove very difficult.

DR. ROWE.—I have been very much interested in food allergy for a great many years, and for some time have tried to determine food sensitizations by the scratch test and with the use of various intradermal extracts alone. Then I began to realize that all the comments on the negative skin reactions that had appeared in the literature were of importance. With that in mind, I gradually evolved the elimination trial diet to help in the determination of those food allergies that are not able to be determined by the skin testing.

I have been using these diets for a number of years with continued help. My paper indicates that I have also continued to use various food extracts for intradermal testing hoping that some would yield dependable information in patients giving negative reactions by the scratch method who were clinically sensitive to specific foods. Up to the present time I have not had so much help from the supplemental use of intradermal tests as I would like.

In recommending trial diets, I have always recommended that diets based on skin reactions should first be tried. If such diets that are based on positive reactions do not give relief, then it is justifiable to use elimination diets or trial diets.

One of the main things I tried to bring out in this paper is the fallibility of many of the commercial extracts that are on the market, and I believe before these extracts are distributed they should be standardized in a way which I have suggested in the paper today.

Dr. Piness was good enough to quote some of the statements I made in 1925. He correctly stated that I had obtained reactions in 91 per cent of these asthmatic patients, but they were not all due to foods. Many reactions were to inhalants, dusts, and pollens. Ninety-one per cent of those patients gave skin reactions, but I did not state that all of those reactions indicated clinical sensitizations.

It is evident that all positive reactions that are obtained need to be checked up by clinical trial, not only with foods but also with inhalants. Many pollen reactions we obtain are not indicative of clinical pollen allergy at all, and many positive food reactions are not indicative of food sensitization. Dr. Piness recently reported that he obtains food reactions in 91 per cent of his cases, which does not correspond with my experience.

DR. PINESS.—We said only 1 case in 100 was sensitive to foods, and foods alone, and that 80 cases in 100 responded to food reactions.

DR. ROWE.—Dr. Parlato wanted to know my position in regard to the intradermal test to foods. It is very important to test a patient first by the scratch test and to follow it if desired by intradermal testing, remembering that many reactions obtained are nonspecific and false and that certain positive reactions do not indicate clinical sen-

sitization. Moreover, food allergy frequently occurs without skin sensitiveness.

I had a similar experience to that of Dr. Kahn about ten or twelve years ago. I tested a patient and got a one-plus reaction to potato and to beef. To check up on the reaction, I did the test intradermally, and this very long-standing asthmatic patient died as a result of the intradermal test. The patient went from one allergic, anaphylactic shock to another and then died. I feel it is very important not to test with a food intradermally the patient who gives good positive reaction to that food by the scratch test.

As I said, I have found trial diet is the real diagnostic tool to use in the diagnosis of food allergy, and that it should be supplemented and modified by skin reactions.

Allergic Relations of Normal and Abnormal Floras of the Intestine. Robert L. Benson, Portland, Ore. (For original article, see page 152.)

DISCUSSION

Dr. Robert W. Lamson, Los Angeles.—Possibly no one in this organization is more qualified than Dr. Benson to do work in the field of so-called bacterial allergy. This term should be qualified when applied to intestinal bacteria, as I shall attempt to point out.

You perhaps remember the English workers who claimed that the cause of asthma in a certain patient was sensitization to his own colon bacillus. Treatment with a vaccine of this organism was associated with a period of improvement in the patient's condition. About two years ago a physician in California published similar results. He also demonstrated skin sensitivity, or at least hyperirritability, to the culture.

Before we attribute specific hypersensitivity to a bacterial culture, it may be necessary to do more than prove the four postulates of Koch. Bacterial allergy is perhaps best typified by the tuberculin reaction. This implies the presence of a tubercle in the body of the reacting individual. This is produced by natural or artificial means with living tubercle bacilli or by the injection of dead ones. Nothing else will induce a specific hypersensitivity to tuberculin.

I am interested in Dr. Benson's report that some of the cultures of intestinal bacteria gave skin reactions on control subjects. One of the residents at the Los Angeles County General Hospital has carried on somewhat similar studies with a group of patients who have complained of severe abdominal discomfort. About 0.02 c.c. of a culture was injected into the skin of the patient from whom the organism had been obtained; a large reaction of the delayed type was obtained. I doubted the specificity of this response, and urged the resident to use himself as a control. I then injected a similar amount in the most superficial layers of the skin of his forearm. Within two hours he had as large a reaction as the one observed on the patient. In addition, he manifested an acute febrile reaction and with it axillary adenopathy. We must keep in mind that specific hypersensitivity to bacteria is one thing, and that local skin irritability may, as in this example, have little connection with etiology. Definite relief was experienced by the above mentioned patient after treatment with this vaccine.

A culture should not be designated an autogenous vaccine solely be-

cause it has been isolated from a patient. The term implies that the organism is related to the etiology of his condition.

Relief from symptoms after treatment with a vaccine is not necessarily proof that it was the causative organism. I have tried to duplicate the results claimed by the English workers, but I have employed a stock typhoid vaccine rather than a vaccine from the patient's colon bacillus. Certain individuals have shown marked improvement in their condition as a result of this treatment. No one would conclude from this that the typhoid bacillus was a primary etiologic factor in the patient's asthma.

I think it is wonderful that Dr. Benson is willing to continue to work in a field that is so confused, and I am sure he will contribute much to our knowledge of hypersensitivity to bacteria.

Dr. E. L. MacQuiddy, Omaha, Neb.—I want to congratulate Dr. Benson, particularly in calling attention to the effect of sodium ricinoleate.

Carrying out the work which I reported last year, we have continued that work, and I think we are now in a position to say that sodium ricinoleate does not change the intestinal flora. We cannot recognize any difference after the administration of huge doses of sodium ricinoleate. We feel definitely that sodium ricinoleate is not absorbed in the intestinal tract and is carried on through and acts locally within the intestinal walls. We do feel now, with our late work which will be published shortly, that it does, however, have an inhibitory reaction upon bacterial activity, and that the amount of ammonia produced in the intestine is lessened by administration of sufficient sodium ricinoleate.

Dr. Milton B. Cohen.—All this knowledge we obtain is always important. This work of Dr. Benson's in fractionating organisms and fractionating out various types of antigens, of course, will some day have some bearing on immunologic problems.

However, I believe we ought to stop, look, and listen a little bit when we hear people talking about specific bacterial allergy, and we should ask them, "Just what do you mean?"

These reactions that Dr. Benson speaks of are, in the main, the reactions of hypersensitive infection. Simply because a patient has allergy and also has an infection, and has a hypersensitivity to that infection, is no evidence, so far as I know, that that individual has an allergic symptom due to the organism from which he is hypersensitive to infection. I have talked this over many times with Dr. Wherry, Dr. Dorst, and the group I was fortunate enough to work with in bacteriology many years ago. Dr. Wherry was kind enough two years ago to send me a series of heat-killed suspensions in which they get these tremendously blown-up arms in some of these unusually hypersensitive cases, with nasal symptoms and other types of allergy, in whom they are able to report they get desensitization and relief.

We followed I do not know how many of these patients, and failed to get any relief for one year's time. My criticism was that they did not know what was going on. We injected them with bacteria and drew some conclusions. We did not get from the series of nasal organisms which he sent us a single good reaction. A reaction like that, yes, occasionally, but the kind of blown-up arms he talked about, with great edemas and skin sensitiveness, we did not see one.

After I sent him the series of reports, he said, "You had better try my intestinal group." I have in my office now the whole group of the normal intestinal flora. You do get an occasional reaction like that. In almost any patient you get a reaction from one of the *B. coli, B. proteus, lactis*, or anything else. We have yet to see a patient in whom we could do anything specifically, in whom we had failed to get relief by any other method.

Furthermore, we have tried autogenous cultures on these individuals, using the term "autogenous" (getting the organism of the patient and assuming that is the one causing the trouble), but we do not get any better results than Rackemann reported. When you give a patient anything that gives local reaction in the arm, you get the result which I expect you get from your vaccine. We use the colon bacillus, and the patient gets a sore arm, which is certainly nonspecific. When you go through all the minutiae of technic which have been described, I think we should be very careful before we draw any conclusions as to the specificity of bacteria in the ordinary allergic states we are usually talking about.

Dr. N. F. Thiberge, New Orleans, La.—I should like to ask the essayist two questions. How is the carbohydrate element separated from the protein element in the culture, and whether he has eliminated the presence of histamine in the culture.

There was a very interesting point brought out at the International Asthma Congress: the presence of histamine in many of the streptococcus cultures.

We have been very much interested in this nonspecific work, and the paper I shall present before the American Medical Association on Thursday will show the action of typhoid protein on a certain number of cases, and histamine in another portion of cases. The question in my mind is whether or not the results we obtain, when we do obtain results from injecting cultures, are due purely to the histamine. A number of years ago we discontinued in our service at the Charity Hospital the use of cutaneous tests with bacterial vaccine. As the reaction appeared in practically all the cases, we found it unnecessary to subject the patient to this extra hardship. I have not tried, however, the carbohydrate element of the culture alone, and I am very eager to know how the essayist separates it so that I can apply it in some of the cases.

Dr. Benson.—I shall have to beg off from any discussion of results here. I will simply state that I disagree with Dr. Cohen on the specificity of these antigens for treatment, as I have found them to a considerable degree specific, and the results have been good. I do not wish to go into any analysis of these, because I have previously presented this and intend to make it the subject of a further report at a future time.

The only point I am attempting to bring out here is a further study on the characteristics of the antigen. I am compelled to say, in answer to Dr. Thiberge's query, that I have not been separating the carbohydrate radical. That work was done at the Rockefeller Institute and at Columbia University, and I have assumed that we can consider the results proved. In an attempt to connect the antigen with clinical results, I do intend to study the bacterial antigens further.

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Dr. Thiberge asked about histamine. I strongly suspect that some of these effects of the so-called normal intestinal flora are due partly to histamine. I wish somebody else would undertake a special study of these organisms in relation to histamine, and try to connect that phase of the subject with the clinical effects observed. So far I have not been able to do it.

I appreciated Dr. Lamson's criticism, and I would mention that while this presentation is on the intestinal flora, it is also applied to other foci, including the sputum.

Constitution and Allergic Manifestations. Tell Nelson, Chicago, Ill.
(For original article, see page 124.)

DISCUSSION

Dr. Robert W. Lamson, Los Angeles, Calif.—I have a criticism to make of Dr. Nelson's charts. We are all prone to make a similar mistake. He has designated the age groups as one to five years, and six to ten years. Statistically, it might be better form to employ the following grouping: (less than) one to four, five to nine, ten to fourteen, etc.

Dr. M. Murray Peshkin, New York City.—It is commonly agreed that percentage figures from a large series of cases can be graphed on a chart to form many different curves. Such graphs, as far as children are concerned, become all the more distorted when the series of cases includes both children and adults.

In Dr. Nelson's series of cases there were 213 children with asthma during the first decade of life; 78 of these children were females and the remaining 135 were males, indicating a sex incidence of 37 and 63 per cent, respectively. These figures conform to the reports of other workers and of myself who have found the sex incidence to be 33⅓ per cent for females and 66⅔ per cent for males.

To speak only of the average age of onset of asthma, especially in children, is of no clinical value. Curves graphically charted indicating the age of onset of asthma are of practical importance. The onset of asthma in children is more frequent at one year than at any other age; and as the children approach the age of ten years, the incidence seems to become progressively less. Children with onset of asthma after ten years of age are relatively uncommon. The latter observation cannot be viewed as a coincidence; considering that this period is the age of puberty, it seems to have some clinical significance.

Dr. Samuel J. Taub, Chicago, Ill.—I should like to have Dr. Nelson clear up one point for me. He showed in his chart great increase in females in the second decade, and he stated that he thought it was probably due to puberty.

I just wonder if it may not be due to more contact at this age with cosmetics or other inhalants, or occupation at that particular period.

Dr. Nelson.—I want to thank Dr. Lamson for bringing to my attention the point of the overlapping of the years in my chart. I showed them as overlapping, but the figures were actually from zero to five, and from six to ten, from eleven to fifteen, and so on. This was an error in charting because of my hurry in making up the slides.

I want to thank Dr. Peshkin for his comments. One who compiles a great many figures can juggle them any way he wants to, to prove his point.

In regard to Dr. Taub's comment on the increase in incidence in the female in the second decade, whether this group was due to inhalants or to occupational contacts rather than to a female hormone or a sexual difference, I cannot say definitely. These cases were just studied from the standpoint of age of onset in the various sexes, and it is perfectly possible it may be due to coming in contact with other irritants with which they have not come in contact before.

Minor Allergy: Its Distribution, Clinical Aspects and Significance. WARREN T. VAUGHAN, Richmond, Va. (For original article, see page 184.)

DISCUSSION

DR. SAMUEL M. FEINBERG, Chicago.—This is a very interesting paper, but it seems to me there are two loopholes left open. One is proof of the fact that some of the minor manifestations are allergic, such manifestations as heart burn, belching, diarrhea, and so forth. The other is the fact, if I heard all the paper, that these manifestations were not checked by allergic diagnosis, by skin tests, or trial methods.

I think we often hear patients give us stories about the effect of certain foods or certain experiences on their symptoms, and when we come to check them closely under controlled conditions we find many are merely mental impressions and psychic effects. I think we should be a little cautious in interpreting those things.

DR. ALBERT H. ROWE, Oakland, Calif.—Several years ago we went to the university and took the histories of a thousand conservative students as they matriculated in the freshman class, and obtained a certain amount of data which are similar to the ones which Dr. Vaughan has presented today. Last year we took another thousand histories to check the results we had obtained.

Our statistics showed that these 2,000 individuals who were questioned in sequence revealed a past history of asthma, hay fever or urticaria in 33 per cent of the cases, and that about 35 per cent gave a positive family history of those three allergic conditions. I did not include any histories of recurrent headaches. Many gave histories which in my mind were indicative of possible gastrointestinal allergy, and they were not included in the numbers that I reported.

I believe, with Dr. Vaughan, that it is very important to take a personal history of food disagreements and dislikes. I agree with Dr. Feinberg certainly that all these histories (and I am sure Dr. Vaughan feels the same way) of dislikes and disagreements do not indicate definite allergic reactions, but they certainly ought to be taken in the routine history by every physician who practices medicine, and those foods ought to be held in suspicion until they can be proved otherwise.

This study Dr. Vaughan has made is really a piece of clinical research, and I think we have to use patients more than we do for research purposes.

DR. FRANCIS M. RACKEMANN, Boston.—It seems to me that Dr. Vaughan's paper shows again that we are working with a variation. At first, I personally used to think about normal people on the one hand, and allergic people on the other, but as a matter of fact, there are many gradations between those not sensitive at all, and those extremely sensitive. In the middle ground, there are people who are slightly sensitive

to one thing or, usually, as Dr. Vaughan says, to a variety of things. I think we shall get farther if we regard the allergic group as simply a variation of the normal group.

DR. VAUGHAN.—I was a little worried about my figures on heredity until I realized I was studying quite a different group from those that had been studied by Cooke and his associates, and by Miss Atkinson, because among those who are classed as nonallergic I had just as strong a family history of allergy as among those who were classed as allergic.

When I did realize that we were really studying a different group, because we were including certain conditions which they had not included, I interpreted it in this way: They have not had allergy, but they have the hereditary predisposition and may develop it at any time in the future.

I am very much interested in Dr. Rowe's figures, because I think it is most interesting that they correspond with ours as closely as they do.

Dr. Feinberg, I am going to read one paragraph, and it is not in the conclusions; it is in the middle. This survey was made by a trained social investigator who had worked with me in my office for some months, and lived in the town where the survey was made.

"It is possible that a survey based upon an exhaustive personal discussion with each patient, together with the indicated sensitization reactions, might show a lower percentage with minor allergy, but I do not anticipate that the difference from our findings would be sufficient to invalidate our conclusions. I recognize the hazard involved in attempting to designate as allergic, recurrent headaches and dermatitis, from the patient's general description, but would once again emphasize the importance in this connection of the patient's ability usually to name definitely the offending agent."

Then there is also this additional factor: I would not consider, as was brought out in the discussion of Dr. Rowe's paper, the negative skin reaction as final evidence against the allergic state.

Workmen Compensation Cases as Seen by the Allergist. SALVATORE J. PARLATO, M.D., Buffalo, N. Y. (Abstract.)

With the tremendous progress which this country has achieved in industry and invention, there has come great improvement in the social and economic welfare of the workman. State legislatures have made provision to continue wages during the time a workman is disabled by any injury which he may suffer while at work. Of late years, the tendency has been to favor the workman. The compensation laws are interpreted broadly and liberally, and controversy sometimes arises as to the nature of the injury and the cause and extent of the disability. The physician's testimony often will determine whether compensation will be given. Compensation laws may vary in the several states. Of interest to the allergist is the fact that awards are made for disablement which is incurred by any process involving contact with acids, alkalies or oils capable of causing dermatitis venenata.

From time to time, changes and even extension of compensation laws will be sought by insurance companies, employers, social service workers and the labor unions. The medical profession should have a directing

hand in formulating any new statutes. It can do much to hold a salutary balance between the one side which desires a too easy and liberal interpretation of the laws and an extension of their provisions which would amount to state medicine, and the other side which would ask for minimal award to the injured workman and a too restricted operation of the laws, especially those which cover occupational diseases.

In this study cases are reported which offer concrete examples where the allergist is called to give expert testimony. In this way, a good part of the clinical and laboratory data on human hypersensitiveness becomes a permanent part of court records. This means the establishment of precedents or test cases by which other disputed compensation claims are settled. Moreover, these test cases are used as arguments for the extension of the provisions of the compensation law. It is therefore very important that caution and conservatism, along with fairness to all concerned, shall be the dominant thought in offering medical testimony by the allergist or any other practicing physician.

DISCUSSION

Dr. Karl D. Figley, Toledo, Ohio.—I wish to congratulate Dr. Parlato on this very timely presentation. I think the industrial commissions are becoming better informed regarding contact dermatitis as it appears in industry, but I do not think they know very much about the constitutional hypersensitiveness.

One of the cases that was included in my report this morning concerns a man who worked in a plate glass factory at Toledo. He claimed that his atopic eczema first appeared in 1925 while he was employed in this factory as an oiler. His job was to lubricate the grinding machinery. This dermatitis then first appeared, according to his statement. He was seen and treated by various dermatologists over a period of several years; as a matter of fact, from 1925 until last month. During all this time he received compensation. To make a long story short, it turned out that this man was hypersensitive to silk, to house dust, to some pollens, and to some foods. The silk was his major hypersensitiveness. He did not have contact dermatitis at all, but he had allergic or atopic eczema.

He changed his job several times, and he got away from the oil. He did bricklaying and had other occupations, and yet the dermatitis persisted. All that time he was paid compensation for his alleged dermatitis from oil, which proved to be no such thing.

Dr. Harry L. Huber, Chicago.—There is another important question that has not been discussed. The allergist should be compensated for his expert testimony. What determines the amount of this compensation?

Dr. Parlato.—I started my paper by saying that the workman is being favored. The compensation law of New York State (I am versed in that one only, and I am sure that the same thing would hold in the other states) provides for what they call expert testimony. It is hoped that it is still the common practice that the one who gives this type of testimony is paid for it. The fee is determined by the presiding officer whether he be a referee in compensation court or a judge in county

court. However, this same officer of any court can issue a subpoena compelling the physician to appear in court and give testimony. While the attending allergist may refuse to give expert testimony unless there has been an arrangement for payment of a considerable fee, the fact remains that he is, thereby, placed in a very embarrassing situation. Should he refuse to testify, he will be placed in a very bad light with the workman and his family. The only thing he can do is to give the desired testimony under protest and trust that he may be later remunerated.

As to Dr. Figley's case, it is true that there are many claims which are made by workmen that are settled in their favor, perhaps unfairly. When I say unfairly, we must remember that there are two people who are mainly concerned in these disputes: one is the employer and the other is the employee. If we are too liberal with awards to the alleged disabled workman, we are liable to endanger the possibility of that man ever getting any other employment. Furthermore, it would mean the raising of the cost of production of that particular product in which he was engaged. Finally, the insurance companies would gradually get their own doctors who might give testimony which would not be so favorable to the workman.

Already there are a great number of disputed compensation cases where the services of an allergist would prove valuable to both sides. I think that gradually the insurance companies as well as the employers are beginning to realize the necessity of consulting with an allergist, not two or three years after a workman has drawn compensation for an alleged disability but as soon as it is practically possible to do so.

The Allergic Nature of the Infantile Diatheses and the Associated Frequency of a Widened Mediastinal Shadow (Thymus?). I. HARRISON TUMPEER, M.D., Chicago, Ill. (Abstract.)

The introduction to this paper is an interesting résumé of the rôle of pediatrics in the early development of the technic employed in allergy. The general contributions of the laboratory worker, internist and other clinicians are mentioned next. Finally, the suggestion is made that the pediatrician has further valuable contributions to make because he has the unique opportunity of observing, recording and studying trends and tendencies which begin in earliest infancy and which he may follow through until adolescence.

In the orientation of the subject it will occur to the pediatrician that the essential symptoms of the allergic constitution have been described by the older observers under the name of the various infantile diatheses.

The records of agroup of babies from private practice were reviewed with a view of determining the incidence of certain findings which occurred so frequently that they seemed to belong to a common larger group. It was found that every baby falling in the classification of the infantile diatheses exhibited several of the following manifestations: widened mediastinal shadow, pylorospasm, craniotabes, eczema, "cradle cap," urticaria, breath holding, "fluttering" respiration, stuffiness of the nose, sneezing, wheezing, stridor, choking spells and noisy nursing, anal spasm, and exaggerated response to disease. The actual statistics

presented were minimal because there had been no attempt to take exhaustive histories. Only those items were recorded which the mother volunteered and which appeared during the examination. This policy avoided the disadvantage of suggestion. Such statistics can only be collected by the pediatrician who sees the babies at successive intervals so that a complete running story is provided, since time must elapse for the development of the various manifestations. Furthermore, the pediatrician is in a position to get the facts before time buries them.

The summary illustrates that the old notion of distinct infantile diatheses is no longer tenable because most of the individual infants manifest the findings of more than one diathesis. The more intelligent conception is impressed on the observer that the idea of diatheses must be discarded before the more intelligent and useful conception offered by allergy. It is concluded that the diathetic infant is an allergic infant.

DISCUSSION

Dr. George L. Waldbott, Detroit, Mich.—I think we have reason to admire Dr. Tumpeer for presenting a paper in which the thymus is mentioned, because at the present time there is so much prejudice against the word "thymus" that any one who rises in a medical society to discuss this subject is liable to be ridiculed.

It is true that many sins have been committed against the thymus gland: some have frequently diagnosed a mediastinal shadow as a thymus on insufficient evidence; even pathologists have made the diagnosis "status thymicolymphaticus" the dumping ground of their unexplained deaths. Nevertheless, I think there is a definite group of cases where no cause of death can be found which show at autopsy an enlarged thymus gland. I have studied thirty-six such cases, and I believe I have some very definite findings, which I have presented elsewhere.

Dr. Anthony of Detroit and I have done another piece of work which is a corollary to that of Dr. Tumpeer inasmuch as we investigated the cases of thirty children who had former x-ray evidence of a large thymus and x-ray treatment over this gland. Among thirty of these children twenty-four turned out to be allergic, and four were questionably allergic, in two only there was no allergic background.

Dr. M. Murray Peshkin, New York City.—Whether or not some or all of the symptoms comprising the "status thymicolymphaticus syndrome" have some bearing on allergy in children is indeed a moot question.

In an unpublished series of about 1,000 children with bronchial asthma, clinical and roentgenographic studies revealed the presence of enlarged thymus in only two patients. (The roentgenograms were taken in the Roentgen-Ray Department, Mount Sinai Hospital, Dr. L. Jaches, Director.) In both cases the symptoms of asthma were cleared after a course of roentgen ray therapy.

In a smaller series of about 150 cases of eczema in infants and children up to eighteen months of age in whom roentgenographic studies of the chest were also made, varying degrees of widening of the mediastinum were frequently noted. Some of these "widened mediastinums" would

make the cases presented on the screen look puny indeed. I recall one patient in whom the widened mediastinum took up three-quarters of the upper chest. From a roentgenographic appearance, a diagnosis of thymic enlargement seemed warranted. However, when the children were fluoroscopically examined, the widened mediastinums were seen to collapse in all excepting two children. Many of the children were followed up with roentgenographic studies. They have gone through various diseases of childhood and have had various operations, especially for the removal of tonsils and adenoids without any disturbances suggestive of the "status thymicolymphaticus make-up." As the children grew older the roentgenographic appearance of the mediastinum was normal. Incidentally, oblique roentgenograms of the mediastinum would have been appreciated in some of the cases shown by Dr. Tumpeer. I believe that a diagnosis of widened mediastinum with the inference that one is dealing with a possible enlarged thymus unconfirmed by other means, should not be entertained.

If Dr. Tumpeer contends his paper is merely an exposition of facts (which according to the presentation is open to serious debate), then the conclusion one may logically arrive at, especially from the roentgenograms presented, is that these so-called facts were merely an expression of opinion based upon personal observations of clinical findings, the interpretation of which can vary and usually does with the observer.

Dr. Samuel J. Levin, Detroit.—About three years ago Doctors Hasley and Jarre of Detroit invented a machine for taking motion x-ray pictures of various organs, including the chest. After running through a series of infants well into the hundreds they found that in practically none of these could they show a persistent mediastinal enlargement, but on ordinary fluoroscopic examination very often a mediastinum was large enough to be called a large thymus.

I think the errors of flat plate and even of fluoroscopic diagnosis of an enlarged thymus gland are very great. So great are they that we read of numerous series of 60 per cent enlarged thymus glands in newborn infants. The last paper on that I think was issued three or four years ago; in the obstetrical department x-ray pictures (flat plates) were made of all the newborn babies, and 60 per cent were reported to have enlarged thymus glands.

Sixty per cent of the human race is not born abnormal. If there is a relationship in the series referred to today between the mediastinal shadow and the allergic constitution, it may be a relationship of function. Anatomically there is nothing to prove the theory of this relationship. The beneficial effect of x-ray therapy may be exerted in an entirely functional manner. I do not contend that these patients treated with x-ray are not benefited. I have seen that happen.

As a pediatrician interested in allergy, and knowing that this paper was to come up, I checked over the few cases of patients with infantile colic and the vomiting who are now more than three years of age. There are twenty-seven of these children whom I have followed from birth who are now more than three years old and whose case histories are accurate enough to report. In only one of these is there anything resembling an allergic manifestation appearing to date. This child had a mild eczema. The incidence seems very low compared to that of the series reported today. My series is probably too small. I think this work needs considerable confirmation before it can be accepted.

DR. C. ULYSSES MOORE, Portland, Ore.—Dr. Tumpeer's statement that babies with pylorospasm develop craniotabes at four months of age is interesting. Does he intend to imply that allergy influences mineral metabolism more than do vitamins?

In the Pacific Northwest about 10 per cent of the newborn infants have flexible parietal bones; over 75 per cent have palpable mastoid fontanelles, and a small percentage have sagittal fontanelles. We reported a series of 193 infants, 62 per cent of whom showed craniotabes before six months of age. None of these had a pathologic mediastinal shadow or a transverse mediastinal dullness greater than 4 cm. at the second interspace. Offhand I cannot state the frequency of pyloric obstruction in this group, but I am certain it was approximately the same as in other infants.

We did not record symptoms of familial allergy in these cases but shall do so in our next series. It was certainly not remarkable. We did record the vitamin intake during pregnancy and found that in human beings, as in experimental animals, an inadequate ingestion of the vitamin B was demonstrably associated with pyloric obstruction.

DR. TUMPEER.—I regret that this discussion has centered about roentgenology instead of allergy. In the presentation I emphasized that we would limit ourselves to the objective finding of a widened mediastinal shadow. That should be plain. For the purpose of cataloging the different signs and symptoms of the infantile diatheses it does not matter whether this widening is tumor, aneurysm or thymus. The discussion has confused and complicated this simple objective fact by discussing the thymus. The discussion further lost itself in the byways of roentgenologic technic. I kept that out of the paper purposely and asked you to assume that the observer's technic and experience were ample because I wanted to keep this paper in the realm of allergy where it belongs.

Since I am forced to discuss roentgenologic aspects, I insist that the discussers should have credited me with enough pediatric experience not to diagnose a widened shadow by flat plates. The roentgenologic reasons for this are very elementary and should not be further elaborated. The diagnosis was made in routine fluoroscopic examination of all babies by the clinician. Routine fluoroscopy provides us with a control which separates the positive from the negative shadows. Fluoroscopy likewise effectively disposes of the suggestion for complicated motion x-ray pictures. The babies are held in the vertical position by a special apparatus. The lateral view plates suggested by Pancoast were not taken due to inexperience with this method. Therefore, we have missed some of these shadows, which appear only in the lateral view. However, this omission makes the statistics presented still more valid because they represent the minimal.

The argument that the thymus disappears at ten years is irrelevant in this discussion. As a matter of fact, practically all of these shadows are found to be absent in treated children when they reach the age of one or two years. Furthermore, we are not discussing the ten-year age group; we are discussing newborn babies and infants. The gentleman who reviewed some records taken from his practice to prepare himself for this discussion, basing his review merely on the title of this paper, should review his material in the light of the facts shown here, because he has not given any evidence to indicate that he was comparing similar ma-

terial, not having seen this tabulation beforehand. He did state that he reviewed selected histories of diathetic children but has not made clear that he practiced routine fluoroscopy. His motion picture x-ray comment falls in similar disrepute before the actual natural motion observed in fluoroscopy. His opinion must be discarded as opposed to observed facts. One man's opinion has no weight against another man's facts. When the subject of the thymus is raised, those devoid of fluoroscopic experience will not rationalize. It seems to become an emotional matter. That is why I avoided the use of the term thymus and substituted the fact of a shadow. Under certain circumstances there may be an honest discrepancy between the thymic findings of different groups with identical roentgenologic technic. In a recent discussion of the question before a pediatric society Grulee suggested that the difference, particularly between European and American, may lie in the geographical distribution, as illustrated by geographical thyroid differences.

It is the purpose of my paper to point out that the signs and symptoms of the various conditions which used to be grouped under the term of the infantile diatheses fit themselves nicely in the pattern of the disturbed constitutional physiology which we call allergy. As a mere associated observation I called attention to the frequency of a widened mediastinal shadow in infants with these findings. This is not a revolutionary idea. It is an old fact but receives such prominence here because it is striking and because it cannot be omitted as one of the common factors in the infantile diatheses or allergy in infancy. This correlation is one of the contributions which the field of pediatrics may make to the field of allergy. Pediatrics has an important application to allergy because the earliest manifestations of allergy present themselves in childhood. During this period the picture is simple and uncomplicated by the permanent changes which occur in the adult. A student with the opportunity in pediatrics of following up trends and tendencies in childhood who has also experience in the field of allergy is in an ideal position to contribute to the latter.

There has been no intention to convince any one of anything in this paper. Least of all, there has been no attempt to convince any one against his will, which is as impossible as to hypnotize a subject against his will. One must be fair and keep an open mind. Useful facts should not be discarded on the basis of opinion. In this case the observed facts of the infantile diatheses suggest the nature of allergy. This conception may clarify a large field of pediatrics. This picture should further dignify and contribute to the usefulness and importance of allergy.

There are two types of papers, one attempts to elucidate a theory based on evidence, requiring further support. The other is an exposition detailing observed facts. This paper is an exposition of facts.

Human Anaphylactic Shock. III. From Substances Other Than Pollen and Serum. GEORGE L. WALDBOTT, Detroit, Mich. (Abstract.)

The author uses the term "human anaphylactic shock" because of the clinical and pathogenic resemblance between the symptoms in sensitive man and the sensitized animal, and because of the uncertainty of present knowledge regarding anaphylactic antibodies. The paper is concerned with anaphylactic shock in man from substances other than

pollen and serum. Twenty-six cases collected from various hospitals and physicians, in which reactions following absorption of such antigens occurred, were assembled. Of these eight are reported which showed the characteristic features of anaphylactic shock. The reactions in the remaining eighteen were due to pulmonary thrombosis, impurities in the infusion apparatus, bacterial contamination of the injected material, toxic effect of the lung, etc.

Of the eight cases with true shock, two were due to nonprotein substances, quinine hydrochloride and methane, and potassium iodide. The symptoms of shock included choking sensation, sneezing, swelling of the face, generalized edema, cyanosis and collapse. Recovery occurred after administration of epinephrin. The third case developed shock after the application of powdered walnut to a scratch on the skin of a two-year-old child. The fourth patient received an accidental intravenous injection of sterile milk. The fifth, a six-month-old boy with eczema developed shock after the first injection of 0.05 c.c. of a 1:100 dilution of rye extract to which he had been proved sensitive. In another patient sensitive to migraine, a typical headache was immediately produced when, after several injections of feather extract, a vein was probably entered. Commercial vaccines appeared responsible for shock in another patient with migraine.

In these cases, the symptoms of shock appeared to be similar to those produced by pollen and serum as well as those seen in the anaphylactic experiment in animals. It is felt that human anaphylactic shock represents a different clinical entity, the recognition of which is of particular importance in the explanation of sudden death of unknown origin. Edema in various parts of the body, particularly in the skin and respiratory membranes is its chief pathologic characteristic.

DISCUSSION

Dr. Albert H. Rowe, Oakland, Calif.—Dr. Waldbott asked me to mention a little child that I have studied for about a year. She gave a large reaction to horse dander, and was also sensitive to mule dander. Her father was a cavalry officer. When she was tested intradermally with mule dander she immediately went into a very severe anaphylactic reaction.

The first thing that occurred was a very marked contraction of the bladder with involuntary urination; she then doubled up with a very severe cramping pain in the abdomen. The next thing was very definite bronchial spasm, followed by a generalized paleness all over her body.

We controlled it very quickly with adrenalin. It took three or four injections over a period of an hour, and we also had to give her two or three other injections later in the evening. The interesting thing was that there was no local reaction. Evidently all the antigen went right into the capillaries, and there was no urticaria at all.

Dr. Samuel J. Taub, Chicago.—I should like to ask Dr. Waldbott how, with the novocaine patients, he could tell whether the symptoms were due to allergic shock or poisoning or maybe an overdose of the

novocaine. I have seen patients who had similar reactions following novocaine injections, especially following large doses of the drug. It seems to me the symptoms resemble more an overdosage of the drug, and they can be largely prevented by giving barbital or its derivatives before the use of novocaine.

DR. WALDBOTT.—As one of my tables indicates, the diagnosis of anaphylactic shock in this case of novocaine death is based on what I believe to be the main feature of human anaphylactic shock, namely pulmonary edema. In addition, there was a tremendous emphysema in the lungs and marked eosinophilia throughout the body. Furthermore, there was a history highly suggestive of allergic rhinitis. In the other case the lungs showed no evidence of edema and emphysema. The patient was dying from tuberculosis, and the physician must have accidentally given an intravenous injection. Death was probably due to the sudden absorption of the whole dose of novocaine in a debilitated patient.

Dr. Rowe's interesting case corroborates my previous observation that any one of the symptoms of allergy may occur during the course of anaphylactic shock. I have brought this out in my paper on shock from pollen injections. However, two symptoms usually predominate, namely, pulmonary manifestations and edema in the skin. In my paper I have pointed to the work of Szauter and Roth which explains why the lung symptoms predominate.

The main point that I wanted to bring out is the complete identity between human and animal anaphylaxis as far as clinical observation is concerned. As in the animal, shock depends on the degree of sensitivity, on the dose, and the mode of absorption. There is also a state of anti-anaphylaxis in man. The same manifestations occur in man as in animal.

DR. PINESS.—I want to say one word to correct Dr. Waldbott. I do not believe he means exactly what he said, that the patient dies in an acute anaphylactic shock showing evidence of pulmonary edema. That is not the opinion of all the men with whom I have discussed the matter, nor is it my opinion of those cases I have seen with pulmonary edema in anaphylactic shock. Pulmonary edema occurs where the symptoms are progressive, and death occurs after a prolonged period. I think Dr. Waldbott's paper bears out that those patients who die suddenly do not get pulmonary edema. Death comes too rapidly. It comes almost immediately with the injection of the substance.

DR. WALDBOTT.—There is very little autopsy material available either to prove or to disprove the opinion of Dr. Piness. Perhaps he will revise his opinion after perusing my tabulation on the pathologic changes in human anaphylaxis which I have collected from the literature in a paper soon to appear in the *American Journal of Diseases of Children*. This indicates that the edema is the most characteristic feature of human anaphylaxis regardless of whether or not death occurs immediately upon the injection. Those of us who have ever injected pollen extract by accident intravenously have seen a generalized edema occur within fifteen to thirty seconds following the injection.